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Original Article

Response of Neoadjuvant Chemotherapy in Triple Negative Breast Cancer and the Impact of Pathologic Complete Response on Survival, an Institutional Research

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ABSTRACT

Objective: To evaluate response of neoadjuvant chemotherapy in Stage I-III triple-negative breast cancer and impact of pathologic complete response on survival.

Study Design: Retrospective longitudinal study.

Place and Duration of Study: Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore Pakistan, from Jan 2006 to Jul 2014.

Methodology: All patients with triple-negative breast cancer who received neoadjuvant chemotherapy were included and data was retrieved from cancer registry of hospital. The patients received neoadjuvant chemotherapy followed by surgery. Radiotherapy was given wherever clinically indicated. Kaplan-Meier and log-rank test was used to calculate survival.

Results: Out of 1113 triple negative breast cancer patients, 150 received neoadjuvant chemotherapy. Mean age was 43±7 years. Fifty-two patients (34.7%) achieved pathological complete response (complete eradication of invasive or in situ carcinoma in breast and axilla (ypT0/is/ypN0) in surgical specimen). Over a median follow up of 61 months, 52 patients (34.7%) had disease progression. Patients with pathological complete response had significantly better 5-years disease-free survival (*p*-value 0.001) and 5-years overall survival (*p*-value 0.002) in comparison to non-pathological complete response group. The 5-years disease-free survival was 90% in pathological complete response group compared to 55% in non-pathological complete response group. Similarly, 5-years overall survival was 94% in pathological complete response group compared to 70% non-pathological complete response group.

Conclusions: Neoadjuvant chemotherapy is an effective treatment modality in management of triple-negative breast cancer. Achievement of pathological complete response is a potential surrogate endpoint as it is associated with significantly better disease-free survival and overall survival.

Keywords: Disease free survival (DFS), Overall survival (os), Pathologic complete response (PCR), Triple negative breast cancer (TNBC)

How to Cite This Article: *Hanif MR, Wahab A, Moeed A, Khan SA, Sheikh RM, Siddiqui N. Response of Neoadjuvant Chemotherapy In Triple Negative Breast Cancer And The Impact of Pathologic Complete Response on Survival, An Institutional Research. Pak Armed Forces Med J 2024; 74(3): 675-679. DOI: https://doi.org/10.51253/pafmj.v74i3.4813*

INTRODUCTION

Breast cancer is the most common type of cancer in women worldwide.[1] It is a heterogeneous disease with variable clinical behavior, response to treatment and prognosis depending on its molecular subtype. Approximately 20% of all breast cancer patients have an aggressive subtype called 'triple negative breast cancer'. Triple negative breast cancer (TNBC) lacks the expression of estrogen receptor (ER), progesterone receptor (PR) and there is neither expression nor the amplification of human epidermal growth factor receptor 2 (Her-2).[2] It is more common among younger premenopausal women, African-American or non-Hispanic black race and is associated with high BMI and BRCA mutations.[3] In comparison with other breast cancer subtypes, TNBCs are predominantly high grade invasive ductal carcinomas and usually presents with larger palpable masses.[4] They are associated with early disease recurrence within the first 2-3 years after treatment and propensity to metastasize to viscera, mainly lungs and brain.[5, 6] Cytotoxic chemotherapy is the mainstay of systemic treatment in TNBC and has more sensitivity to neoadjuvant chemotherapy regimens than other breast cancer subtypes.[6, 7]. Despite overall poor prognosis, survival is comparable to other breast cancer subtypes, if pathologic complete response (pCR) is achieved.[6] A number of studies have demonstrated that TNBC patients who achieve pCR, experience better DFS and OS than the patients with residual disease 6,.[8-10]. Considering the outstanding prognostic importance of pCR, it is considered to be an important surrogate endpoint in clinical trials assessing the efficacy of neoadjuvant chemotherapy.[6-9]. The objective of this

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Received: 17 Jul 2020; revision received: 25 Sep 2020; accepted: 06 Oct 2020

study was to analyze pathologic complete response and survival outcomes of neoadjuvant chemotherapy in TNBC in our population.

METHODOLOGY

The retrospective longitudinal study was carried out at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC) Lahore, Pakistan, after approval by the Institutional Review Board [EX-05-07-19-02]. The Hospital's electronic database was queried from January 2006 to July 2016 to identify all patients with a diagnosis of stage I–III TNBC who received neoadjuvant chemotherapy.

Inclusion Criteria: Women aged >18 years with biopsy proven triple negative breast cancer and who received therapy were included.

Exclusion Criteria: Patients were excluded from the study if they had received treatment previously for breast cancer, had non-invasive breast cancer or any malignancy other than breast cancer.

Medical records of 1113 TNBC patients were reviewed; out of which 150 patients with complete information on clinical stage and receptor status were identified who received NACT. Data was collected for clinical stage according to TNM staging AJCC 8th edition, tumor grade, NACT regimen, type of surgery, date of surgery, pCR, use of radiation therapy, date of recurrence, date of last follow up and date of death. ER and PR status was assessed by immunohistochemistry (IHC) and tumors with less than 1% stained cells were considered to have negative receptor status. HER-2 status was assessed by either IHC or fluorescent in situ hybridization (FISH). HER-2 negativity was defined as either lack of HER2 gene amplification (FISH) or a score of 0 or 1+ (IHC). The pCR was defined as the lack of invasive or in situ carcinoma in breast and axilla (ypT0/is/ypN0) in surgical specimen at definitive surgery.[11]

Statistical Package for Social Sciences (SPSS) version 20.0 was used for the data analysis. Mean±standard deviation was computed for continuous variables while frequencies and percentages were reported for categorical variables. The disease-free survival (DFS) was defined as the time from date of definitive surgery to date of first relapse. The overall survival (OS) was defined as time from date of definitive surgery to time of death of any cause or last follow-up. The Kaplan-Meier method was used to estimate survival as a function of time, and survival differences was analyzed by using log-rank test. Statistical significance was defined as a two-tailed with of p-value ≤ 0.05.

RESULTS

We screened 1113 TNBC patients and identified 150 patients with stage I–III who were treated with neo-adjuvant chemotherapy. The mean age of the study population was 43 years (standard deviation of ± 7) with 88 patients (58.6%) being < 45 years. Baseline characteristics of patients are shown in Table-I.

One hundred and twenty-five patients (82%) had tumor sizes ≤T2 and 27(18%) had tumor sizes >T2. All patients had invasive ductal carcinoma and out of them 120(80%) were grade III tumors. Seventy-two patients (48%) had clinically involved axillary nodes. Ninety-eight (65%) patients underwent breast conservation surgery (BCS) whereas remaining had mastectomies. All patients received adjuvant radiotherapy, except one who had disease progression before radiotherapy. Different chemotherapy regimens were used, as reported in Table-II. One hundred and fifteen patients (77%) received Anthracyclines-Taxane based chemotherapy and out

of them 106 patients (92%) received sequential therapy. Thirty-five patients (23%) received other different neoadjuvant regimens.

Out of 150, fifty-two patients (34.7%) achieved pathologic complete response

(pCR). With respect to chemotherapy regimens, sequential Anthracyclines-Taxane based regimens were associated with the higher pCR rate (34%) and among them adriamycin, cyclophosphamide plus paclitaxel (AC/Taxol) was the most effective one (pCR rate 41%). The clinical T and N stage were inversely related to pCR rate. The pCR rate for tumors ≤T2 was 36.6% compared to 26% for tumors >T2. However, the proportion of patients with tumor size >T3 were much less than ≤T2. Among node negative patients, pCR rate was 41% compared to only 28% in node positive patients.

Over a median follow up of 61 months (range; 2-145 months), 52 patients (34.7%) among 150 experienced disease progression. In pCR group (n = 52), only 5 (9.6%) had disease progression whereas in non-pCR group (n = 98), 47 patients (48%) experienced disease progression. The 5-years DFS and OS were 63% and 80% respectively, as shown in Figure-1.

In pCR group, survival outcomes were significantly better than patients with residual disease. The 5-years DFS was 90% in pCR group compared to 55% in non-

pCR group. Similarly, 5-years OS was 94% in pCR group compared to 70% non-pCR group as shown in Figure-2.

The baseline nodal involvement also affected survival outcomes with respect to achievement of pCR. In node negative patients, 5-years DFS and OS were 90% vs 60% and 95% vs 72% in pCR and non-pCR group respectively. Node positive patients who achieved pCR, experienced better 5-years DFS and OS compared to non- pCR group (95% vs 42% and 95% vs 65% respectively).

Table-I: Triple Negative Breast Cancer patient's characteristics (n=150)

Variables	Categories	n(%)
Age (years) Mean±standard deviation 43.±7.0		
Family History	No	114(77.0)
	Yes	34(23.0)
Grade	II	30(20.0)
	III	120(80.0)
Histology	IDC	145(96.7)
	IDC + DCIS	5(3.3)
Clinical stage	I	2(1.3)
	IIA	63(42.0)
	IIB	67(44.7)
	IIIA	12(8.0)
	IIIB	4(2.7)
	IIIC	2(1.3)
Clinical tumor size	T1	5(3.3)
	T2	118(78.7)
	T3	23(15.3)
	T4	4(2.7%)
Clinical nodal status	N0	78(52.0%)
	N1	65(43.3%)
	N2	5(3.3)
	N3	2(1.3)
Surgery type	Breast-conserving Surgery	98(65.3)
	Mastectomy	52(34.7)

(IDC: invasive ductal carcinoma; DCIS: ductal carcinoma in-situ)

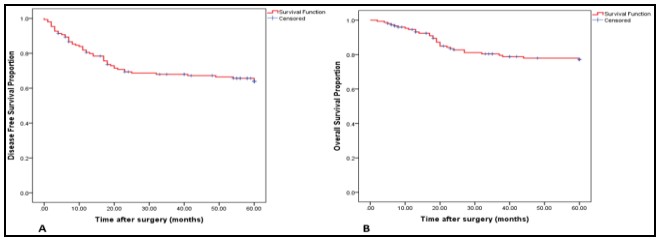

Figure-1:(A) 5-years Disease-free survival (B) 5-years Overall survival

DISCUSSION

TNBC is an aggressive subtype of breast cancer that lacks targeted therapy and systemic treatment is limited to chemotherapy. TNBC is more chemosensitive than other breast cancer subtypes with higher pCR rates in neoadjuvant settings. Conventionally, anthracyclines-taxane based regimens have been the most optimal chemotherapy regimens.[12] With the development Next Generation Sequencing (NGS), molecular classification of TNBC has been done and novel targets are under investigation.[13-15] Cumulative evidence from review of large randomized clinical trials has shown that neoadjuvant and adjuvant chemotherapies have similar results in terms of disease free survival (DFS) and overall OS.[16,17] However, the role of neoadjuvant chemotherapy has much evolved in recent decades as it allows more breast conservations and enables prompt assessment of treatment response.[18-20] Several neoadjuvant trials have demonstrated that achievement of pCR is associated with improved DFS and OS. Therefore, it is considered a potential surrogate endpoint for long-term survival in TNBC.

Table-II: Chemotherapy Regimens (n=150)

Variables	Categories	Tn(%)
Sequential Anthracyclines + Taxane		106(70.7)
	AC/Taxol	35(33.0)
	AC/DOC	48(45.0)
	FEC/DOC	23(22.0)
Concomitant Anthracyclines + taxane		9(6.0)
	TAC	9(100.0)
Miscellaneous		35(23.3)
	FAC	20(57%)
	AC	9(26%)
	FEC	4(11%)
	TC	2(6%)

AC: doxorubicin/Cyclophosphamide, DOC: Docetaxel, FEC: 5-Fluorouracil/Epirubicin/Cyclophosphamide, TAC: Docetaxel/Doxorubicin/Cyclophosphamide, FAC: 5-Fluorouracil/Doxorubicin/Cyclophosphamide, TC: Docetaxel/Cyclophosphamide)

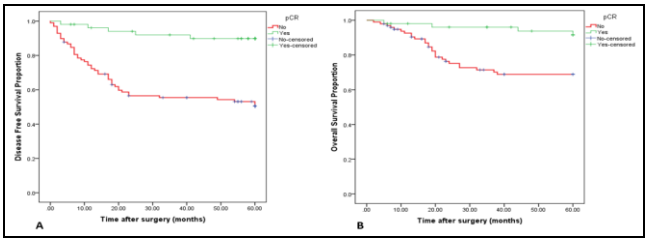

Figure-2 (A): Disease free survival with respect to pCR (pathological complete response) (B) Overall survival with respect to pCR (pathological complete response)

Majority of our study population received sequential anthracyclines with taxane based che-

motherapy regimens and 52 patients (34.7%) achieved pCR. The highest pCR rate in our study was observed in AC/Taxol group (41%). This is in accordance with international literature that has reported pCR rates ranging from 22-45% in TNBC with use of anthracyclines-taxane based regimens.[6-11]. Liedtke *et al*. in their prospective study at M.D. Anderson Cancer Centre published in 2008 reported that TNBC patients have higher pCR rates than other breast cancer subtypes (22% vs 11%; *p*-value 0.034).[6] The patients who achieved pCR had very good survival comparable to other breast cancer subtypes than those who have residual disease. The 3-years OS was 94% in pCR group compared to 68% in patients with residual disease.[6] Cortazar and colleagues in a large, pooled analysis of 12 international randomized neoadjuvant chemotherapy trials in breast cancer (the CTNeoBC pooled analysis) studied association between pCR and long-term survival. TNBC and Her-2 positive patients who achieved pCR, experienced significantly better event free survival (EFS) and OS than with residual disease.[8]

Similarly, Symmans *et al*. have reported that TNBC patients who achieve pCR after NACT, had significantly better 10-years relapse free survival compared to patients with residual disease (86% vs 23%).[10] Fisher *et al*. in their retrospective study comparing neoadjuvant and adjuvant chemotherapy in TNBC have reported OS of 92.3% for patients achieving pCR after NACT and 67.2% in patients with residual disease.[21] Although, survival outcomes were comparable in NACT and adjuvant treatment groups, important to note is tumors with high-risk features were included in NACT group.

The findings in our study are consistent with international literature depicting the predictive value of pCR on long-term survival outcomes. Our study also demonstrated that the patients who achieved PCR, experienced significantly better 5-year DFS and 5-year OS (90% vs 55% and 94% vs 70% respectively) compared to patients with residual disease. The patients with positive axillary nodes experienced comparable survival to node negative tumors after achievement of pCR.

A number of clinical trials have been done in recent decades to find the treatment regimens achieving higher pCR rates. On the basis of finding that TNBC demonstrates increased sensitivity to DNA-damaging agents, the efficacy of carboplatin has been evaluated in different neoadjuvant trials.[22, 23] The Cancer and Leukemia Group B (CALGB) 40603 trial showed significantly increased pCR rates in breast (60% vs 44%) and axilla (54% vs 41%) by addition of carboplatin to the standard chemotherapy regimen containing dose dense AC/Taxol . The GeparSixto 66 trial used paclitaxel, liposomal doxo-rubicin and bevacizumab with or without weekly carboplatin. The pCR rate was 53% in those treated with additional carboplatin compared to 37% in treated without carboplatin. The 3 years follow up of GeparSixto study demonstrated improved DFS in TNBC patients randomized to carboplatin, but at the cost of associated increased hematological toxicity and dose reductions.[24] Although numerically the pCR rate was increased with addition of carboplatin in both studies but neither of these two studies was powered to demonstrate the EFS and DFS differences. Although, the impact of addition of carboplatin on survival outcomes with achievement of pCR is still to be established, we suggest the use of additional carboplatin to standard chemotherapy regimens in selected patients. We think it would be a suitable practice in young fit patients with locally advanced disease to achieve better local control of disease in the form of pCR. As only conventional chemotherapy regimens were used in our study, the pCR rate was comparatively lower than demonstrated in recent clinical trials.

LIMITATIONS OF STUDY

Selection bias was an important limitation of our study. We had a skewed population with young fit patients as per institutional acceptance criteria for treatment at SKMCH & RC. This might have affected the survival results demonstrated in our study. Further, BRCA testing was not available by that time in our institute, so we lack the information and treatment response in possible BRCA positive patients.

CONCLUSIONS

Our study has shown the benefit of NACT in TNBC patients in terms of improved survival with achievement of pCR, in concordance with other neoadjuvant studies. Outcome is worse in patients with residual disease in breast and/or axilla in terms of significantly lower DFS and OS. So NACT is helpful to identify the chemoresistant patients (i.e. those who have not achieved pCR) and consider them for salvage treatments as residual disease. Further trials are needed to develop novel neoadjuvant approaches in TNBC patients to increase pCR rates.

Conflict of Interest: None.

Authors Contribution

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

MRH & AW: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

AM & SAK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

RMS & NS: Conception, data acquisition, drafting the manuscript, approval of 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 investigated and resolved.

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