DOI: 10.7860/JCDR/2024/65849.19320

Original Article

Oncology Section

Pathological Complete Response with Platinum Containing Neoadjuvant Chemotherapy in Triple-negative Breast Cancer: An Interventional Study

BINILA MARY JOSE[1], VR AJITH KUMAR[2], SUMA SUSAN MELOOT[3]

ABSTRACT

Introduction: Triple-negative Breast Cancer (TNBC) accounts for 20% of all breast cancer cases globally and responds well to cytotoxic chemotherapy. The standard Neoadjuvant Chemotherapy (NAC) regimen for TNBC includes 4+4 cycles of anthracycline, cyclophosphamide, and taxane. Integrating platinum agents into the NAC has gained attention as an effective treatment for TNBC.

Aim: To estimate the proportion of pathological Complete Response (pCR) in TNBC patients receiving platinum-based NAC.

Materials and Methods: This interventional study enrolled 73 non metastatic TNBC patients who attended the radiotherapy Outpatient Department (OPD) of Government Medical College Thiruvananthapuram Kerala, India from April 2022 to April 2023. All patients underwent a complete history, physical examination, and tumour histopathology with Oestrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor 2 (HER2) receptor status assessment. Patients were treated with the NAC regimen: Epirubicin 90 mg/m^2, Cyclophosphamide 600 mg/m^2 intravenously every three weeks for four cycles followed by Paclitaxel 175 mg/m^2, Carboplatin according to Area Under Curve (AUC)-5 by intravenous administration every three weeks for four cycles. Clinical response was evaluated after the completion of NAC using Response Evaluation Criteria in Solid Tumours (RECIST) criteria. pCR assessment was conducted postsurgery. Study variables were entered into Microsoft Excel, and the analysis was performed using Statistical Packages for Social Sciences (SPSS) version 24.0.

Results: Out of 73 patients with a mean age of 54.4 years, 33 (45.2%) patients showed complete response on clinical examination after eight cycles of Carboplatin-containing NAC, and 23 (31.5%) patients achieved pCR. Total 30 (41.1%) patients experienced complications during chemotherapy, with neutropenia and peripheral neuropathy being the most common, each occurring in 22 (30.1%) patients.

Conclusion: In present study, one-third of the patients achieved pCR with platinum-based NAC with an acceptable side-effect profile. It represents a beneficial treatment option for TNBC patients; however, the impact of pCR on survival requires further validation through long-term studies. Given the poor prognosis and limited treatment options for TNBC, the addition of affordable and available agents to the existing chemotherapy regimen could potentially revolutionise the treatment of these patients.

Keywords: Breast neoplasms, Carboplatin, Response evaluation criteria in solid tumours

INTRODUCTION

Among Indian females, breast cancer has become the number one cancer, with an age-adjusted rate as high as 25.8 per 100,000 women and a mortality rate of 12.7 per 100,000 women [1]. Globally, TNBC, characterised by the absence of expression of Oestrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2), accounts for 20% of all breast cancer cases. In the Indian scenario, this percentage is even higher, around 31% of all breast cancer cases. Currently, cytotoxic chemotherapy remains the only systemic treatment option for TNBC [2]. Various experimental therapies have been developed as Neoadjuvant Chemotherapy (NAC) for TNBC which could elicit better treatment response The standard NAC regimens for TNBC include 4+4 cycles of anthracycline, cyclophosphamide, and taxane. Recently, the integration of Deoxyribonucleic acid (DNA)-damaging agents, such as platinum drugs, into NAC has garnered attention as a potentially effective treatment for TNBC. The mechanism of action of platinum analogs involves attacking cancer cells by inducing DNA double-strand breaks. BRCA1 (BReast CAncer gene1)-associated breast cancers and TNBC share common pathogenic features, with many TNBC patients exhibiting alterations in BRCA1 function. This suggests that TNBC may be highly sensitive to interstrand cross-linking agents. Pathological Complete Response (pCR), defined as the absence of residual cancer in the breast or lymph nodes following NAC surgery, has been associated with a reduced risk of systemic recurrence and serves as an effective biomarker of treatment response after NAC [3]. A higher pCR is linked to improved clinical outcomes, including a decreased need for axillary surgery, increased likelihood of breast conservation surgery, and better recurrence-free survival rates [4]. Therefore the quest for enhancing PCR has fueled interest in evaluation of neoadjuvant drugs ,with pCR following platinum containing chemotherapy as a primary endpoint in present study. Clinical response is assessed following the RECIST criteria 1.1 [5].

The primary objective of present study is to estimate the proportion of pCR after NAC for TNBC using platinum-containing compounds in patients attending the radiotherapy Outpatient Department during the study period. Additionally, the study aims to document treatment response according to RECIST criteria and record the incidence of adverse effects following treatment.

MATERIALS AND METHODS

This interventional study was conducted over a period of one year from April 2022 to April 2023. The study population included all patients with TNBC meeting the inclusion criteria and attending the

radiotherapy Outpatient Department of Government Medical College Thiruvananthapuram, Kerala, India who were willing to participate in the study. Ethical considerations were taken into account, with Institutional Ethical Committee clearance obtained (IEC no: 03/17/2022/MCT), informed consent obtained from all participants, and confidentiality maintained throughout the study. The allocation of patients for neoadjuvant platinum-containing chemotherapy was done by the treating oncologist.

Inclusion criteria:

- Biopsy-proven cases of breast cancer that were ER, PR, and HER2 negative
- Stage II-III TNBC according to the Tumour Node Metastasis (TNM) staging (8th edition) [6]
- No history of previous cancer therapies
- Normal cardiac and renal function
- No co-morbidities precluding systemic chemotherapy/ radiotherapy
- Normal bone marrow reserve
- Eastern Cooperative Oncology Group (ECOG) scores 0-2 [7].
- Patients less than 70 years of age
- Patients planned for the neoadjuvant chemotherapy regimen: Epirubicin, Cyclophosphamide, Paclitaxel, and Carboplatin as per the treating doctor's recommendation

Exclusion criteria:

- Patients with metastatic breast cancer
- Pregnant or nursing mothers
- Patients with bilateral breast cancers

Sample size calcualtion: The sample size was calculated based on the formula N=(1.96x1.96)PQ/l^2, where 'P' is the prevalence, 'Q' is (100-P), and 'l' is the relative proportion of P P=58 (according to the parent study-BrighTNess trial in which 92 of 160 patients i.e., 58% showed complete pCR in the carboplatin-paclitaxel arm. Therefore n=69.54, sample size calculated was 73, considering a 5% dropout rate [8].

Study variables: Patient characteristics included age, co-morbidities and ECOG status [7]. Tumour characteristics, and treatment characteristics were documented. Treatment response was assessed using RECIST criteria 1.1, and toxicity assessment was done using Common Terminology Criteria for Adverse Events V5.0 Nov 27, 2017 [5,9]. The main outcome studied was Pathological Complete Response (pCR).

Outcome measures: The pCR was defined as the absence of residual invasive and in situ cancer in the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant chemotherapy [10]. Toxicity assessments were graded for neutropenia, thrombocytopenia, peripheral neuropathy, and vomiting based on severity levels.

Study Procedure

Patients meeting the selection criteria were enrolled in the study after obtaining informed consent. The baseline performance status of all patients was recorded according to ECOG guidelines. Treatment details and investigations were documented in a master file and proforma. All patients underwent a thorough evaluation, including a complete history, physical examination, and confirmation of triple-negative breast cancer status (ER, PR, HER2 negative). Metastatic disease activity was ruled out through appropriate investigations. Laboratory investigations, such as complete blood counts, renal function tests, liver function tests, electrolytes, and 24-hour urine creatinine clearance, were conducted. Tumours were staged according to TNM staging criteria.

Patients in the study received NAC with Epirubicin 90 mg/m^2, Cyclophosphamide 600 mg/m^2 intravenously every three weeks for four cycles, followed by Paclitaxel 175 mg/m^2 and Carboplatin according to AUC-5 intravenously every three weeks for four cycles [11]. Any chemotherapy-related adverse events during the treatment cycles were noted. After completion of NAC, the disease was clinically reassessed, and treatment response was evaluated according to RECIST 1.1 criteria. Data were collected post-Modified Radical Mastectomy (MRM) from histopathology reports, and any pathologic complete response achieved was recorded.

STATISTICAL ANALYSIS

The data were entered into Excel and analysed using SPSS version 24.0 Categorical variables were presented as frequency and percentage. The association between categorical variables was assessed using the Chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 73 patients were included in the study and all of them were closely followed-up and available for response assessment.

A) **Patient characteristics:** In present study, most patients 33 (45%) were in the age group of 50-60 years, with a mean age of 54.4 years. All patients were female. The majority of 56 patients were postmenopausal (76.7%), 31 (42.5%) were hypertensive, and 30 (41.1%) were diabetic. Total 13 (13.7%) patients had a family history of breast cancer. Only patients with ECOG performance status of 0-2 were included in the study, with 60 (82.2%) having performance status 1.

B) **Tumour characteristics:** Most patients 41 (56%) had right-sided breast cancer, and the rest had left-sided disease. The majority of tumours were in the upper outer quadrant 43 (58.9%), followed by 16 (21.9%) in the lower outer quadrant and 14 (19.2%) in the upper inner quadrant. Most patients had invasive ductal carcinoma 41 (56.2%), with the remaining cases being invasive lobular carcinoma 25 (34.2%) and invasive carcinoma-NST 7 (9.6%). The majority were T3 stage 47 (64.4%), N1 stage 44 (60.3%), and non metastatic cases [Table/Fig-1]. Composite staging showed 43.8% in stage IIIA, 28.8% in stage IIIB, 1.4% in stage IIIC, and 26% in stage IIB [Table/Fig-2].

T stage	Percentage	N stage	Percentage	M stage	Percentage
T2	5.5 (4/73)	N0	27.4 (20/73)	MO	100
T3	64.4 (47/73)	N1	60.3 (44/73)		
T4	30.1 (22/73)	N2	11 (8/73)		
		N3	1.4 (1/73)		

[Table/Fig-1]: Distribution of TNM stages in the study.

Composite stage	Frequency	Percentage
II B	19	26
III A	32	43.8
III B	21	28.8
III C	1	1.4
Total	73	100

[Table/Fig-2]: Composite stage.

C) **Treatment-related factors:** Total 30 (41.1%) patients developed one or more adverse events during chemotherapy, while 43 (58.9%) patients tolerated chemotherapy without adverse events [Table/Fig-3]. Prophylactic Granulocyte Colony Stimulating Factor (GCSF) was given to 42 (57.5%) patients. Total 95% patients had a complete clinical response, while 54.8% had a partial clinical response. Total 23 (31.5%) patients achieved a pCR following NAC.

Neoadjuvant Chemotherapy (NAC): All patients in the study underwent MRM following NAC and it was found that 23 patients achieved pCR that accounted for 31.5 percentage (with 95%

Complications	Frequency	Percentage
Neutropenia	22	30.1
Grade-1	7	31.8
Grade-2	4	18.2
Grade-3	11	50
Thrombocytopenia	7	9.5
Grade-1	6	85.7
Grade-2	1	14.2
Peripheral neuropathy	22	30.1
Grade-1	22	100
Vomiting	5	6.8
Grade-1	5	100

[Table/Fig-3]: Complications during chemotherapy.

confidence interval; 20.8-42.2) of patients. pCR was not obtained in the remaining 50 patients (68.5%). It was found that among the 33 patients who achieved complete clinical response as per RECIST, 23 of them achieved pCR (69.7%) whereas the remaining 10 patients (30.3%) did not. The association between clinical complete response and pCR was found to be statistically significant (p<0.001) [Table/Fig-4].

Complete clinical response as per RECIST criteria post NACT	pCR obtained				Total		χ^2	Df	p-value
	Yes		No						
	N	%	N	%	N	%			
Yes	23	100	10	20	33	45.2			
No	0	0	40	80	40	54.8	40.70	1	<0.001
Total	23	100	50	100	73	100			

[Table/Fig-4]: Complete clinical response as per RECIST vs pCR.

Factors Influencing Response to NAC:

A) **Initial T stage and pCR:** A statistically significant association was found between higher T stages and pCR (p=0.003) [Table/Fig-5].

B) **Initial N stage and pCR:** No statistically significant association was found between N stage and pCR [Table/Fig-6].

C) **Initial composite stage and pCR:** A statistically significant association was found between composite stage and pCR (p=0.001) [Table/Fig-7].

D) **Menopausal status and pCR:** No statistically significant association was found between menopausal status and pCR [Table/Fig-8].

T stage	pCR obtained				Total		χ^2	df	p-value
	Yes		No						
	N	%	N	%	N	%			
T2	0	0	4	8	4	5.5			
T3	10	43.5	37	74	47	64.4			
T4b	13	56.5	9	18	22	30.1	11.88	2	0.003
Total	23	100	50	100	73	100			

[Table/Fig-5]: Initial T stage and pCR.

N stage	pCR obtained				Total		χ^2	df	p-value
	Yes		No						
	N	%	N	%	N	%			
N0	5	21.7	15	30	20	27.4			
N1	12	52.2	32	64	44	60.3			
N2	5	21.7	3	6	8	11			
N3	1	4.3	0	0	1	1.4	6.49	3	0.090
Total	23	100	50	100	73	100			

[Table/Fig-6]: Initial N stage and pCR.

Composite stage	pCR obtained				Total		χ^2	df	p-value
	Yes		No						
	N	%	N	%	N	%			
II B	0	0	19	38	19	26			
III A	10	43.5	22	44	32	43.8			
III B	12	52.2	9	18	21	28.8			
III C	1	4.3	0	0	1	1.4	17.31	3	0.001
Total	23	100	50	100	73	100			

[Table/Fig-7]: Initial composite stage and pCR.

Menopausal status	pCR obtained				Total		χ^2	Df	p-value
	Yes		No						
	N	%	N	%	N	%			
Postmenopausal	15	65.2	41	82	56	76.7			
Premenopausal	8	34.8	9	18	17	23.3	2.48	1	0.115
Total	23	100	50	100	73	100			

[Table/Fig-8]: Menopausal status and pCR.

DISCUSSION

The TNBC is known for its aggressive nature and response to cytotoxic chemotherapy. NAC in TNBC has been extensively studied in clinical trials with the aim of achieving better outcomes, particularly in terms of achieving a pCR [12]. In present study, which focused on estimating pCR in TNBC patients receiving platinum-based NAC, 73 patients were enrolled, with a mean age of 54.4 years. A higher proportion of postmenopausal patients were included compared to other similar studies such as the GeparSixto trial, BrighTNess trial, and I-SPY 2 trial [8,13,14].

The tumour characteristics observed in present study were consistent with previous studies, with the majority of patients having stage II and III TNBC with invasive ductal carcinoma as the predominant histologic type. After completion of NAC, all 73 patients in the study showed a response, with 45% achieving a complete clinical response according to RECIST criteria. The study found a pCR rate of 31.5%, which was lower compared to a meta-analysis by Poggio F et al., that reported a pCR rate of 52% [12]. However, the results were similar to an earlier study by Alba E et al., which also reported a pCR rate around 30% [11].

The chemotherapy schedule in present study was similar to that in the study by Alba E et al., involving four cycles of Anthracycline and Cyclophosphamide followed by Taxane and Carboplatin [11]. The study size of 73 patients was smaller compared to other phase III studies, which may have impacted the results. Improved rates of pCR have been shown to have a positive impact on event-free survival and overall survival in TNBC patients, as demonstrated by previous studies [15]. Anthracycline and taxane-based NAC have been associated with higher pCR rates and better survival outcomes in TNBC patients [16,17].

Future studies may benefit from careful patient selection, including BRCA genetic mutation testing and molecular profiling, as well as making modifications to chemotherapy regimens, such as adding PARP inhibitors or immunotherapy to platinum-based NAC, which have shown promising results in achieving higher pCR rates in TNBC patients.

Limitation(s)

An important limitation of present study was its small sample size. Additionally, the absence of a control group hindered ability to assess the specific effect of adding carboplatin to the anthracycline-taxane backbone. Furthermore, due to financial and technical constraints, we were unable to conduct testing for BRCA mutation and molecular profiling, thereby limiting authors' ability to study the impact of carboplatin in the BRCA mutated subtype with deficient DNA repair mechanisms.

CONCLUSION(S)

One-third of patients in present study achieved a pCR with platinum-based NAC, with an acceptable side-effect profile, suggesting it as a beneficial treatment option for TNBC patients. However, further validation is needed to determine the impact of pCR on overall survival. The main limitations of present study were the small size of the cohort and the lack of a control group for comparison.

Acknowledgement

Authors extended their deep and sincere gratitude to all mentors for providing invaluable guidance throughout the study. Authors are grateful for the support of all the faculty members in the department who assisted in completing present study. Authors acknowledge the support from the Journal of Clinical and Diagnostic Research (JCDR) team in preparing present manuscript.

REFERENCES

[1] Malvia S, Bagadi SA, Dubey US, Saxena S. Epidemiology of breast cancer in Indian women. Asia Pac J Clin Oncol. 2017;13(4):289-95.
[2] Wang D, Feng J, Xu B. A meta-analysis of platinum-based neoadjuvant chemotherapy versus standard neoadjuvant chemotherapy for triple-negative breast cancer. Future Oncol. 2019;15(23):2779-90.
[3] Sparano JA. Neoadjuvant systemic therapy for breast cancer: Searching for more effectively curative therapies. JAMA Oncol. 2018;4(3):293-95.
[4] Berry DA, Hudis CA. Neoadjuvant therapy in breast cancer as a basis for drug approval. JAMA Oncol. 2015;1(7):875-86.
[5] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
[6] Brierley JD, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. 8th Edition. Wiley-Blackwell; December 2016;272.
[7] ECOG Performance Status Scale [Internet]. ECOG-ACRIN Cancer Research Group. [cited 2023 Jan 17]. Available from: https://ecog-acrin.org/resources/ecog-performance-status/.
[8] Loibl S, O'Shaughnessy J, Untch M, Sikov WM, Rugo HS, McKee MD, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): A randomised, phase 3 trial. Lancet Oncol. 2018;19(4):497-509.
[9] Common Terminology Criteria for Adverse Events (CTCAE). November 27, 2017. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.
[10] Cortazar P, Geyer CE. Pathological complete response in neoadjuvant treatment of breast cancer. Ann Surg Oncol. 2015;22(5):1441-46.
[11] Alba E, Chacon JI, Lluch A, Anton A, Estevez L, Cirauqui B, et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006-03, multicenter study. Breast Cancer Res Treat. 2012;136(2):487-93.
[12] Poggio F, Bruzzone M, Ceppi M, Pondé NF, La Valle G, Del Mastro L, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: A systematic review and meta-analysis. Ann Oncol. 2018;29(7):1497-508.
[13] von Minckwitz G, Schneeweiss A, Loibl S, Salat C, Denkert C, Rezai M, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): A randomised phase 2 trial. Lancet Oncol. 2014;15(7):747-56.
[14] Rugo HS, Olopade OI, DeMichele A, Yau C, van 't Veer LJ, Buxton MB, et al. Adaptive randomization of Veliparib-Carboplatin treatment in breast cancer. N Engl J Med. 2016;375(1):23-34.
[15] Geyer CE, Sikov WM, Huober J, Rugo HS, Wolmark N, O'Shaughnessy J, et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. Annals of Oncology. 2022;33(4):384-94.
[16] Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet. 2014;384(9938):164-72.
[17] Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med. 2020;382(9):810-21.

PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Radiotherapy, Government Medical College, Thiruvananthapuram, Kerala, India.
2. Associate Professor, Department of Radiotherapy, Government Medical College, Thiruvananthapuram, Kerala, India.
3. Assistant Professor, Department of Radiotherapy, Government Medical College, Thiruvananthapuram, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Suma Susan Meloot,
Assistant Professor, Department of Radiotherapy, Government Medical College, Thiruvananthapuram-695011, Kerala, India.
E-mail: suma.sm2009@gmail.com.

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 07, 2023
- Manual Googling: Sep 12, 2023
- iThenticate Software: Feb 01, 2024 (8%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 07, 2023**
Date of Peer Review: **Sep 02, 2023**
Date of Acceptance: **Feb 03, 2024**
Date of Publishing: **Apr 01, 2024**