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Original Research Article

DOCETAXEL VERSUS DOCETAXEL PLUS CAPECITABINE AS NEOADJUVANT CHEMOTHERAPY FOR TRIPLE-NEGATIVE BREAST CANCER PATIENTS

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Abstract: *Triple-negative breast cancer (TNBC) poses a significant risk of metastasis and relapse, demanding effective neoadjuvant chemotherapy strategies. This retrospective study aimed to compare the outcomes of a sole docetaxel versus a docetaxel and capecitabine combination (TX) regimen as a neoadjuvant treatment for triple-negative breast cancer. The current retrospective analysis was conducted at the oncology department of Nishtar Hospital Multan and encompassed 80 randomly assigned female patients with triple-negative breast cancer between September 17, 2021, and December 31, 2022. They were further divided into two groups. The TX regimen (docetaxel 75 mg/m2 d1 with capecitabine 800 mg/m2 twice d1-14, q3w) was given to forty patients in the first group named the TX group, where the T regimen (docetaxel 75 mg/m2 d1 q3w) was given to other forty patients assigned in the second group called as T group, over four cycles. The primary endpoint was achieving a pathological complete response (pCR) in the breast, with secondary objectives including pCR in both the breast and axilla, invasive disease-free survival (iDFS), overall 0ne year survival (OS), and safety assessments. In the retrospective analysis, 21 patients in the TX group and 5 in the T group achieved pCR (52.5% vs. 12.5%, p=0.014), demonstrating a statistically significant superiority of the TX regimen. The TX regimen substantially increased pCR incidence (95% CI 2.3-47.1%; p = 0.028) within a subgroup characterized by a high Ki-67 level. The TX group showed a higher incidence of hand-foot syndrome and a statistically insignificant (p > 0.05) incidence of alopecia, presenting a manageable toxicity profile. Comparable iDFS and OS rates were observed in both groups throughout the 12-month average follow-up period. This retrospective analysis indicates that the TX regimen yielded significantly superior results, with a marked increase in pCR rates, particularly in the high Ki-67 subgroup. The observed toxicity profile was manageable, emphasizing the clinical benefits of incorporating capecitabine with docetaxel in neoadjuvant chemotherapy for triple-negative breast cancer patients.*

Keywords: Triple Negative Breast Neoplasms, Neoadjuvant Therapy, Docetaxel, Capecitabine, Pathological Complete Response

Introduction

Triple-negative breast cancer (TNBC) presents a formidable challenge due to its heightened risk of metastasis and relapse(Fabbri et al., 2020), necessitating effective neoadjuvant chemotherapy strategies. (Carvalho, 2023). An optimal chemotherapy regimen is pivotal in achieving favorable outcomes (Thall et al., 2000). This retrospective study delves into the comparative analysis of two neoadjuvant chemotherapy regimens—sole docetaxel versus a combination of docetaxel and capecitabine (TX)—to determine their impact on pathological complete response (pCR) rates in patients with TNBC.

TNBC, characterized by the absence of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2, lacks targeted therapies, making neoadjuvant chemotherapy a critical component in its management. (Gupta et al., 2020). Understanding the comparative efficacy and safety of different chemotherapy regimens is essential for optimizing treatment outcomes in TNBC patients.

With TNBC's aggressive nature and limited therapeutic options, identifying the most effective neoadjuvant chemotherapy regimen becomes imperative.(Medina et al., 2020) The need for a nuanced understanding of the outcomes associated with different treatment strategies, such as the sole use of docetaxel versus its combination with capecitabine, underscores the significance of this study.

While docetaxel has shown efficacy in TNBC, adding capecitabine may further enhance treatment responses. This study aims to address this gap in knowledge by comparing the two regimens in terms of achieving pCR, a crucial indicator of treatment success. Exploring additional endpoints, such as invasive disease-free survival (TFS) and overall one-year survival (OS), adds depth to evaluating treatment outcomes.

The rationale for this study lies in its potential to guide clinicians in selecting the most effective neoadjuvant chemotherapy regimen for TNBC patients. By elucidating the comparative benefits and safety profiles of the docetaxel-only and docetaxel-capecitabine combination, this research contributes valuable insights to optimize therapeutic approaches and improve outcomes for TNBC patients.

Methodology

This retrospective analysis was conducted at the oncology department of Nishtar Hospital Multan. The study spanned the period between September 17, 2021, and December 31, 2022, and aimed to assess the outcomes of neoadjuvant chemotherapy in female patients diagnosed with triple-negative breast cancer (TNBC).Eighty female patients with confirmed TNBC were randomly selected for inclusion in

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the study. To ensure robust analysis, patients were divided into the TX group (receiving docetaxel and capecitabine combination) and the T group (receiving sole docetaxel). Patients with incomplete data were excluded from the analysis.

Both groups received initial chemotherapy with four cycles of Adriamycin and cyclophosphamide, after which The TX group (n=40) received a combination regimen consisting of docetaxel at a dose of 75 mg/m2 on day one and capecitabine at a dose of 800 mg/m2 twice daily on days 1-14, administered every three weeks for a total of four cycles. The T group (n=40) received sole docetaxel at a 75 mg/m2 dose on day 1, following the same three-week cycle for four cycles. The study's primary endpoint was achieving pathological complete response (pCR) in the breast. Secondary endpoints included pCR in both the breast and axilla, invasive disease-free survival (iDFS), overall one-year survival (OS), and safety assessments.

Comprehensive data on patient demographics, histological types, clinical tumor (CT) and nodal (N) stages, Ki-67 levels, and treatment-related information were collected from patient records. Adverse events were documented to assess the safety profile of each regimen. A detailed molecular subgroup analysis explored the differential treatment response within subgroups defined by age, initial CT and cN stages, and Ki-67 levels.

This study adhered to ethical guidelines, and approval was obtained from the institutional review board. Informed consent was obtained from all participants, and patient confidentiality was strictly maintained throughout the study. Statistical analysis was performed using appropriate tests, including chi-square tests for categorical variables and t-tests for continuous variables. A p-value less than 0.05 was considered statistically significant.

Results

The present study was done at Nishtar Hospital Multan's oncology department and included 80 randomly selected female participants with triple-negative breast cancer diagnosed between September 17, 2021, and December 31, 2022. A total of 91 adult females with diagnosed triple-negative breast cancers were taken into the study. Eleven patients were excluded due to insufficient data available regarding these patients. As a result, 80 individuals were assessed for the main Endpoint (TX: 40; TE: 40).

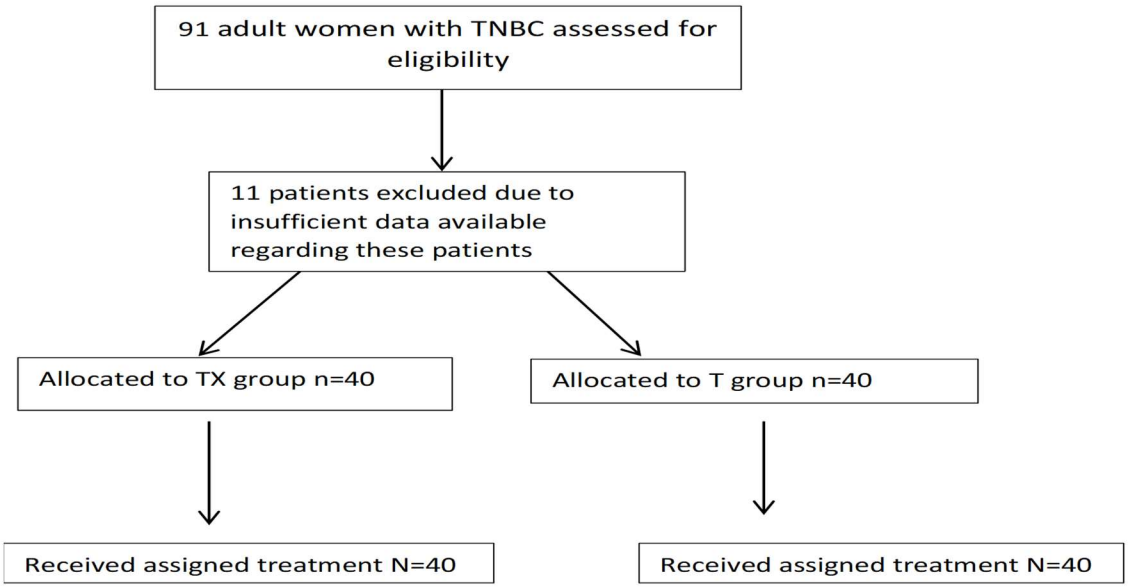

Fig 1 shows the study flowchart.

Table 1 shows the general data of the 80 participants who got the assigned treatments.

Variable	Total N=80(n,%)	TX group n=40(n,%)	T Group n=40 (n,%)	*P*-value
Age				
Less than 50	44(55)	25(62.5)	19(47.5)	0.074
Greater than 50	36(45)	15(37.5)	21(52.5)	
Histological type				
No specific type	70(87.5)	36(90)	34(85)	0.478
Invasive lobular	5(6.25)	2(5)	3(7.5)	
Mixed	5(6.25)	2(5)	3(7.5)	

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Initial CT stage				
Ct0	3(3.75)	2(5)	1(2.5)	0.548
Ct1	5(6.25)	1(2.5)	4(10)	
Ct2	62(77.5)	33(82.5)	29(72.5)	
Ct3	7(8.75)	3(7.5)	4(10)	
Ct4	3(3.75)	1(2.5)	2(5)	
Initial cN stage				
N0	8(10)	5(12.5)	3(7.5)	0.375
N1	32(40)	19(47.5)	13(32.5)	
N2	35(43.7)	14(35)	21(52.5)	
N3	5(6.25)	2(5)	3(7.5)	
Ki67				
Less than 20	55(68.75)	28(70)	27(67.5)	0.698
Greater than 20	25(31.25)	12(30)	13(32.5)	

Table 1 shows the demographic features of the 80 patients who got the assigned treatments. The two groups were balanced in terms of patient and treatment characteristics. The whole population's median age ranged from 21 to 78 years. The TX group had fewer elderly patients (> 50: 37.5% versus 52.5%). CT stage 2 was most prevalent in both groups, as shown in Table 1.

A comprehensive molecular subgroup assessment was done to determine the possible advantage of the TX regimen over the t regimen. PCR was attained by 21 patients in the TX group and 5 in the T group (52.5% vs. 12.5%, p=0.014). The table below compares subgroups among the two study groups (Figure 2).

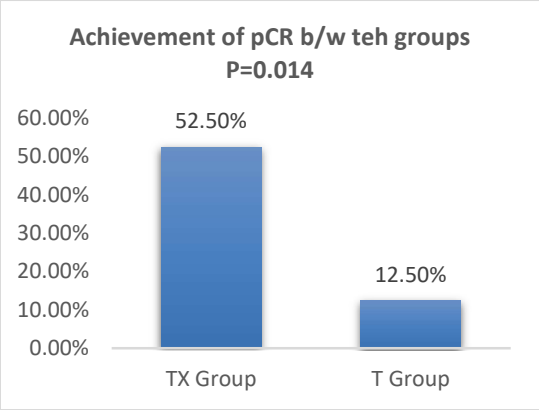

Figure 2: Difference between the group in achievement of pathological complete response (pCR)

33% of individuals over 50 in the TX group achieved PCR, whereas the rate was meager in the corresponding T group, which was a mere 4.7%. Similarly, the results were better in patients younger than 50 years, with PCR in the TX group ranging up to 64% and just 21% in the T group. In the TX group with ki67 less than 20, PCR was achieved by 57% of the patients, whereas the rate was meager in the corresponding T group, which was only 11%.PCR rate in the initial ct stage T0-T1 in the TX group was 66%, while in T2-T4, it was 51%. The rates were meager in the T group, being 20% in the T0-T1 stage and just 11 % inT2-T4 stage; similarly, the rates of PCR in the TX group were higher in the cN stage N0-N1 than in the T group, as shown in the table mentioned above.

Comparable but slightly better iDFS and OS rates were observed in the TX group throughout the 12-month average follow-up period. One year, iDFS rates were 91% (95% CI 77.5–94.5%) in the TX group while 81.1% (95% CI 74.5–93.7%). One year OS rates were 96.7% in the TX group as compared to 83.6% rate in the T group, as shown in Table 3.

Table 4 demonstrates the side effects encountered in both study groups. Both groups had comparable side effects, with the TX group having a slightly more significant percentage of incidences than the T group. The incidence of hand-foot syndrome was 60% in the TX group and just 35% in the T group. During the follow-up period, neither group experienced any symptomatic cardiac events. Both regimens resulted in a significant rate of neutropenia (TX: 60%; TE: 42.5%). Alopecia was less common in the T group than in the TX group. (70% vs. 82%).

Table 2: Subgroup analysis between TX and T group:

Variable	**TX Group**		**T Group**	
	Patients	PCR	Patients	PCR
Age				
Greater than 50	15	5(33.3)	21	1(4.76)
Less than 50	25	16(64)	19	4(21.0)
Initial CT stage				
T0-1	3	2(66)	5	1(20)
T2-4	37	19(51.35)	35	4(11.4)
Initial cN stage				
N0-1	24	16(66.6)	16	3(18.75)
N2-4	16	5(31.25)	24	2(8.33)
Ki 67				
Less than 20	28	16(57.1)	27	3(11.11)
Greater than 20	12	5(41.6)	13	2(15.38)

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Table 3: Survival Analysis among both groups

Variable	TX Group		T Group	
	Percentage	95% CI	Percentage	95% CI
iDSF (1year)	91%	77.5–94.5%	81.1%	74.5–93.7%).
OS	96.7%	91.5–98.5%	83..6	82.7–91.6%

Table 4: Side effects among both groups

Variable	TX group N=40		T group N=40		P value
	Any grade (n, %)	Grade 3-4 (n, %)	Any grade (n, %)	Grade 3-4(n, %)	
Neutropenia	24(60)	10(25)	17(42.5)	12(30)	0.352
Anemia	11(27.5)	2(5)	8(20)	1(2.5)	0.214
Hand foot syndrome	24(60)	12(30)	14(35)	3(7.5)	0.845
Sensory neuropathy	16(40)	4(10)	14(35)	2(5)	0.145
Heart failure	0	0	0	0	-
Alopecia	33(82)	-	28(70)	-	0.91
Wound infection	3(7.5)	0	2(5)	0	0.158
Leukemia	2(5)	0	1 (2.5)	0	0.124

Discussion

The retrospective analysis comparing the neoadjuvant chemotherapy regimens—sole docetaxel versus the combination of docetaxel and capecitabine (TX)—in treating triple-negative breast cancer (TNBC) presents valuable insights into treatment outcomes and safety profiles. The study focused on achieving a pathological complete response (pCR) as the primary endpoint, shedding light on the comparative efficacy of the two regimens.

The findings revealed a statistically significant superiority of the TX regimen over sole docetaxel, with a notable increase in pCR rates (52.5% vs. 12.5%). This considerable difference suggests that adding capecitabine to docetaxel improves treatment responses. Subgroup analysis further highlighted the advantage of the TX regimen, particularly in patients over 50 years, younger patients, those with high Ki-67 levels, and specific initial CT and cN stages. The TX group exhibited higher pCR rates in these subgroups, indicating a broad positive impact.

TX was shown to be very effective for cancer of the breast, and it did not compromise long-term survival. It was discovered that TX might be a viable option for patients who are suitable for neoadjuvant chemotherapy.

Capecitabine is efficacious and well-managed in breast cancer patients with metastatic disease (Chan et al., 2009; O'Shaughnessy et al., 2002), and 14 trials have investigated its use in the adjuvant period. GeparQuattro (Von Minckwitz et al., 2014), US Oncology 01,062(O'Shaughnessy et al., 2015), FinXX and his colleagues' (Joensuu et al., 2017) experimented with further capecitabine to the typical treatment. Yet, other assessments like GEICAM/2003-10 (Lluch et al., 2020) and CALGB 49,907 (Muss et al., 2019) utilized capecitabine as a substitute, CREATE-X employed a neoadjuvant framework to pick vulnerable non-PCR patients to boost treatment (Masuda et al., 2017), and in further present-day investigations, CBCSG10 and SYUCC001 limited its applications in the TNBC subtype(Li et al., 2020; Wang et al., 2021). Several meta-analyses(Li et al., 2013; Natori et al., 2017) found that adding capecitabine did not enhance iDFS or OS in not selected individuals, although it did significantly enhance mortality in the TNBC subgroup

In our study, TX exhibited a much greater pCR incidence than T in a subgroup of people with an elevated Ki-67 score (pCR: 41.6% vs. 15.38%). Ki-67 is a proliferation indicator, and earlier research has found that greater Ki-67 levels are related to a worse prognosis and indicate a better treatment response (Chen et al., 2018; Hong et al., 2021; Jones et al., 2009; Lee et al., 2008; Li et al., 2013; Natori et al., 2017; Pistelli et al., 2021; Rouzier et al., 2005; Tao et al., 2017). The mechanism behind enhanced capecitabine sensitivity in malignancies with an elevated proliferation rate remains unknown. The Ki-67 index, on the other hand, is linked to thymidine phosphorylase activity (Kitabatake et al., 2002), a critical stimulation enzyme for capecitabine (Andreetta et al., 2009). In addition, capecitabine has a reduced influence on the immune system produced from bone marrow and may operate as an immune modulator (Zhang et al., 2021). This property may account for its decreased hematological damage and the possibility of two-week continuous dosing. We predicted that these properties enable capecitabine to continually reduce tumor cells while acting as an immune modulator in the tumor's microenvironment, critical for quickly proliferating malignancies. More evidence, however, is required to corroborate these findings and our theory. TNBC patients have an unsuccessful outcome due to the severe nature of the disease and the absence of endocrine and standard anti-HER2-targeted treatment (Perou et al., 2000). Platinum (Geyer et al., 2022), PD-1/PD-L1 inhibitors (Schmid et al., 2020), and poly (ADP-ribose) polymerase antagonists (PARPi) (Gonçalves et al., 2020) have recently been used in routine chemotherapy. However, these novel escalation therapies are linked with distinct short- and long-term harmful effects, suggesting that tolerance may be an issue in subsequent decision-making.

According to our findings, the pCR for the neoadjuvant TX for TNBC was 52.5 %, a significant response for this subtype. It seems that TX could represent a neoadjuvant alternative for some TNBC patients. TX generated a greater frequency of hand-foot syndrome (60%) and baldness 82% with a controllable toxicity profile, which was similar to a recent metastatic illness study (Chan et al., 2009). TX is believed to be less likely to induce uncommon severe long-term side effects like heart failure and secondary malignancy.

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Our study had significant limitations due to the early conclusion of the trial, the relatively small sample size, and the lagging statistical evaluation. However, the results for specific subtypes were still appealing and justified an additional investigation.

Conclusion

Based on a retrospective study, the TX treatment regimen led to better outcomes, with a significant increase in pCR rates, particularly among patients with a high Ki-67 status. The reported toxicity profile was manageable, highlighting the benefits of combining capecitabine and docetaxel in neoadjuvant therapy for triple-negative breast cancer.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department Concerned.
Consent for publication
Approved
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Not applicable

Conflict of interest

The authors declared absence of conflict of interest.

Author Contribution

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Conception of Study, Development of Research Methodology Design, Study Design,, Review of manuscript, final approval of manuscript
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Conception of Study, Development of Research Methodology Design, Study Design,, Review of manuscript, final approval of manuscript
SARA KHAN (Senior Registrar)
Manuscript revisions, critical input.
Coordination of collaborative efforts.
***ASMA MASOOD** (Pharmacist)*
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ABDULMANAN
Data entry and Data analysis, drafting article.
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Data acquisition, analysis.
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