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ORIGINAL ARTICLE

Neoadjuvant Docetaxel Plus Carboplatin Versus Epirubicin Plus Cyclophosphamide Followed by Docetaxel in Triple-Negative, Early-Stage Breast Cancer

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ABSTRACT

Objective: To evaluate the safety and efficacy of epirubicin and cyclophosphamide followed by docetaxel versus docetaxel and carboplatin chemotherapy in triple-negative, early-stage breast cancer (TNBC).

Methodology: A prospective study was conducted in the oncology ward of Nishtar Hospital, Multan, from 3rd Mar 2021 to 3rd Mar 2022. A total of 70 TNBC women were included in the study and were divided into two groups. Group DC (35 patients) was administered docetaxel plus carboplatin and then underwent a mastectomy. Group ECD (35 patients) was administered epirubicin plus cyclophosphamide followed by docetaxel underwent mastectomy. Both groups received radiotherapy after mastectomy.

Results: In group A, 21 patients (60.0%) achieved a pCR (95% CI 46.0-74.3), 13 patients (38.1%) achieved a pCR (95% CI 23.1-52.0). The difference between both groups was 21.9% (OR 2.49, 95% CI 2.2-42.5; p=0.002); hence non-inferiority was met. DCb regimen showed improved results compared to the EC-D regimen (p=0.039). After 1-year follow-up, it was observed that overall survival and event-free rates did not differ significantly between both groups.

Conclusion: Docetaxel along with carboplatin demonstrated higher pCR than that of anthracycline and taxane-based treatment regimens. However, no significant difference was found between the two in terms of overall survival and event-free survival. Surprisingly, docetaxel and carboplatin caused a higher incidence of treatment-associated adverse effects.

Keywords: Chemotherapy, radiotherapy, mastectomy, triple-negative breast carcinoma.

INTRODUCTION

Triple-negative breast carcinoma (TNBC) patients have a poor prognosis because of the absence of targeted treatment. Despite the advent of the new treatment options for primary breast carcinoma, basic treatment for TNBC remains cytotoxic chemotherapy. Neoadjuvant therapy is often suggested for TNBC. There are many pros of neoadjuvant therapy like reduction in tumor size and breast-conserving operation, avoiding dissection of axillary lymph node, evaluating chemosensitivity of the tumor in vivo, and turning inoperable tumors into operable. Standard therapy for TNBC is anthracycline and taxane-based neoadjuvant treatment. This leads to longer event-free survival (EFS) and overall survival (OS) in subjects achieving pathologic complete response (pCR) [1, 2]. Moreover, as chemotherapy is the main form of treatment for TNBC, there is a gap in the literature on the role and significance of adjuvant radiotherapy [3]. However, a study stated that in TNBC patients adjuvant radiotherapy after mastectomy led to superior event-free survival (EFS) versus mastectomy alone [4].

Researchers have been consistently focusing on improving the pCR rate in TNBC patients. Platinum induces breaks in double-stranded DNA thus attacking cancerous cells, TNBC may be responsive to platinum [5]. According to the studies, when neoadjuvant chemotherapy is modified with the addition of carboplatin, the pCR rate of TNBC improves significantly [6, 7]. As anthracycline-based regimes cause cardiotoxicity in the long term, many studies have evaluated the effectiveness of taxanes plus carboplatin neoadjuvant regimes and found that PCR rates were satisfactory [8, 9]. However, the impact of anthracycline and taxane-based regime versus docetaxel plus carboplatin without anthracycline on TNBC was not assessed in any study. In this study, we will evaluate the safety and efficacy of epirubicin and cyclophosphamide followed by docetaxel versus docetaxel and carboplatin chemotherapy in TNBC.

METHODOLOGY

This prospective clinical trial was conducted in the oncology ward of Nishtar Hospital, Multan, for 2 years from 3rd Mar 2021 to 3rd Mar 2022. The patients with the following characteristics were consecutively enrolled in the study: age more than 18; having histologically or cytologically confirmed invasive TNBC, and stage II or III cancer which isn't previously treated. All the patients were reevaluated through immunohistochemistry, fluorescence testing, blood analysis, and imaging tools (ultrasound, mammography, and MRI). Cancer staging was done through the chest or abdominal CT scan and abdominal sonography. Patients with malignancy at another site or who had already received anticancer treatment were excluded from the study. All patients were informed of study objectives and their informed consent was sought. Similarly, ethical approval of the study was taken from the ethical committee of the hospital.

All included patients were allotted a computer-generated number and were randomly allocated in two groups. Patients in group DC were administered 75 mg/m^2 of docetaxel and carboplatin intravenously every three weeks for 6 cycles whereas those in the ECD group were given 90mg/m^2 of epirubicin and 600mg/m^2 cyclophosphamide intravenously every three weeks for 4 cycles. During the treatment protocol, hematological and biochemical analysis was conducted at every cycle. In the case where adverse events were reported, the chemotherapy dose was reduced. After 3-8 weeks of the last neoadjuvant chemotherapy, surgical intervention was performed. The type of surgery performed, whether breast-conserving surgery or mastectomy, remained the discretion of the treating surgeon. Patients from both groups received radiotherapy postmastectomy at 40 Gy five days a week and for 3 weeks.

The primary endpoint of the study was the pCR rate, defined as the loss of invasive tumor cells in the axilla and breast. Whereas, the secondary endpoints were OS, EFS, and treatment-associated toxicities.

SPSS (version 21) was used for statistical analysis.

RESULTS

A total of 70 women qualified for the study and were divided into 2 study groups. The median age of patients was 46.5 years (range: 19-62 years). The patients in the two groups didn't differ significantly in terms of cancer characteristics. The majority of patients in both groups had grade III tumors (45, 64.2%), positive nodal involvement (40, 53.3%), and had to undergo mastectomy (54, 72%) (Table 1).

In DC group 21 patients (60.0%) achieved a pCR (95% CI 46.0-74.3) whereas 13 patients (38.1%) in ECD group achieved a pCR (95% CI 23.1-52.0). The difference between both groups was 21.9% (OR 2.49, 95% CI 2.2-42.5; p=0.002); hence non-inferiority was met. DCb regimen showed improved results compared to the ECD regimen (p=0.039). In terms of cancer stages, 72% (18 out of 25) patients with clinical stage II disease in the DC group achieved pCR while 45.8% (11 out of 24) patients in the ECD group achieved pCR with this status (95% CI 2.3–39.7; p = 0.031) while the remaining pCR achievers in both groups had stage III disease (95% CI -10.5- 49.6; p = 0.384).

Table 1: Characteristics of cancer in both groups (N=70)

Variables	DC (N=35)	ECD (N=35)	P-value
Age, median (Q1, Q3) years	49 (37, 56)	45 (41, 59)	0.09
	Tumor grade		
I/II	12 (34.2%)	13 (38%)	
III	23 (65.7%)	22 (62%)	0.64
	Tumor size		
T1/T2	25 (71%)	27 (77%)	
T3/T4	10 (29%)	8 (23%)	0.75
	Nodal involvement		
Positive	21 (59%)	19 (55%)	
Negative	14 (41%)	16 (45%)	0.72
	Clinical stage		
II	25 (71%)	24 (69.7%)	
III	10 (29%)	11 (31.3%)	0.92
	Breast-conserving surgery		
Yes	9 (26%)	7 (21%)	
No	26 (74%)	28 (79%)	0.82

Table 2: Treatment-associated toxicities in study groups (N=70)

Toxicities	DC (N=35)	ECD (N=35)
Anemia	14 (41%)	13(37.1%)
Thrombocytopenia	6 (17.6%)	2 (5.4%)
Neutropenia	10 (28.5%)	7 (21%)
Constipation	8 (23%)	7 (21%)
Diarrhea	10 (29.8%)	9 (26.5%)
Nausea	13 (37.1%)	12 (34.1%)
Vomiting	9 (27.3%)	8 (22.5%)
Edema	5 (15.4%)	9 (26.5%)
Fatigue	13 (37.5%)	14 (41.4%)
Bone pain	8 (23.2%)	16 (45.4%)

Following 15 months median follow-up duration (range: 14-22 months), OS and EFS were found to be similar in 2 groups: 2-year EFS rate for DC group was 91.3% (95%CI 81.2–97.5%) and for ECD group was 87.6% (95% CI 75.4– 99.7%) (p= 0.71) whereas 2-years OS rate of DC group was 94.5% (85.5–100%) compared with 92.6%

(84.8–100%) of ECD group (hazard ratio (HR) 0.94, 95% CI .15– 5.12, p =.92).

Table 2 represents the toxicities associated with the treatment regime in each study group. DC group was reported to demonstrate a higher rate of toxicities than in ECD group.

DISCUSSION

By definition, TNBC is defined as a condition characterized by the absence of ER, PR, and Her2. Among various treatment strategies, cytotoxic chemotherapy is considered most effective. TNBS is significantly responsive to cytotoxic chemotherapy and exhibits a raised pCR rate following neoadjuvant chemotherapy. However, TNBC has high clinical progression than non-TNBC [10, 11]. Therefore, the above study aimed to evaluate the capacity of neoadjuvant therapy in improving the pCR rate and the prognosis of the disease.

Over time, anthracycline and taxane-based neoadjuvant regimes have been adopted as a standard treatment for TNBC. According to some clinical trials, the addition of platinum in these regimes considerably improves the pCR rate. In a study, a higher pCR rate (53%) was achieved by the study group who was administered with carboplatin in combination with paclitaxel, bevacizumab, and doxorubicin as compared to the other group who were not given carboplatin [12]. In another trial, patients were randomly allocated into two groups where one group was given carboplatin plus paclitaxel while the other administered paclitaxel. Both the treatment regimes were followed by the administration of cyclophosphamide plus doxorubicin. Similar to the previous study, the carboplatin receiving group demonstrated a higher pCR rate (p=0.003) [7]. Sibylle Loibl et al. conducted a randomized, double-blind trial and found that the patients receiving carboplatin, paclitaxel, and veliparib reported a higher pCR rate than those who received paclitaxel alone (53% vs 31%, p<0.0001). However, the pCR rate was almost similar to the third group who took carboplatin plus paclitaxel (58%, p=0.36) [6]. The results of this study augmented the role importance of carboplatin in the treatment of TNBC. However, combining carboplatin with paclitaxel and anthracycline has been reported to increase the toxicity rate such that only 64-88% of patients complete their treatment cycles [12]. Given the established long-lasting cardiotoxicity resulting from an anthracycline, the majority of studies assessed the efficacy of neoadjuvant carboplatin plus taxanes regimes for treating TNBC patients and satisfactory results have been achieved [8]. Earlier china-based studies reported a pCR rate of 57.9% following administration of carboplatin plus paclitaxel in 4 cycles to TNBC patients [8]. Sharma et al. explored the efficacy of carboplatin plus docetaxel and found out that pCR and residual cancer burden rate of 55% and 68%, respectively [9]. Similarly, in other studies, the pCR rate of the DC regime seems to be higher than that of anthracycline and taxane-based neoadjuvant regimes [13, 14].

In the above-described study, we found out that the combination of docetaxel with carboplatin for 6 cycles helped in the achievement of a higher pCR rate (60%) whereas the ECD group reported pCR rate of 38%. These results comply with the results of multiple previous studies. According to a prospective, randomized, multi-center study 6 cycles of DC regime was found to be tolerable with a pCR rate of 88.6% [15].

Out study reported significantly improved EFS and OS in patients who achieved pCR following neoadjuvant treatment in both groups which goes hand-in-hand with the findings of a previous meta-analysis [1]. However, another subgroup analysis, found that carboplatin has a superior response to TNBC than that of docetaxel (p=0.03). Therefore, further subgroup analysis is required in this regard.

Limitation of the study: The study is limited in terms of smaller study size and limited follow-up period. Therefore, retrospective studies are recommended to analyze the long-term effects of the treatment regimes.

CONCLUSION

Docetaxel along with carboplatin demonstrated higher pCR than that of anthracycline and taxane-based treatment regimens. However, no significant difference was found between the two in terms of overall survival and event-free survival. Surprisingly, docetaxel and carboplatin caused a higher incidence of treatment-associated adverse effects.

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