

## **Comparative Analysis between an Anthracycline Based Regimen and a Platin Based Regimen in Neoadjuvant Setting for Triple-negative Breast Cancer: A Single Institutional Retrospective Study**

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### **Authors' contributions**

*This work was carried out in collaboration with all authors. Author SB tabulated the raw data for the research and wrote the manuscript while author RJ designed the study. Statistical analysis was the result of the effort of author KBC. Author Shilpi Adhikary performed an extensive literature search. Author Santanu Acharyya dealt with the revisions during peer review procedure. The work flow of the entire research work was performed under the supervision of group leader author CD who finalized and approved the manuscript.*

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### **ABSTRACT**

**Objective:** This study was designed to comparatively analyse the response and survival between Carboplatin plus Paclitaxel (TP) vs. 5FU plus Epirubicin plus Cyclophosphamide (FEC) in ER, PR and HER-2 neu negative Breast Cancer patients of locally advanced breast cancer (LABC), large operable breast cancer (LOBC) and selected early breast cancer (EBC) patients as Neoadjuvant Chemotherapy (NACT).

**Methods:** In this single institutional retrospective study total 73, AJCC 7th Stage group IIB ~ IIIB, TNBC patients were included. Patients received 6 cycles of either Inj. Paclitaxel 175 mg/m<sup>2</sup> IV plus Inj. Carboplatin at an AUC 5 IV on day1, every 21 days or Inj. 5FU 500 mg/m<sup>2</sup> IV plus Inj. Epirubicin 100 mg/m<sup>2</sup> IV plus Inj. Cyclophosphamide 500 mg/m<sup>2</sup> IV on day1, every 21 days.

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Response was assessed after 6 cycles using RECIST v1.1. Modified Radical Mastectomy (MRM) and adjuvant Post Mastectomy Radiation Therapy (PMRT) were done as and when indicated. Survival benefit was comparatively analysed in terms of median progression free survival (mPFS) and Overall Survival (OS).

**Results:** Out of total 73 Triple-negative Breast Cancer(TNBC) patients 37 (3 EBC, 11 LOBC and 23 LABC) received FEC and 36 (2 EBC, 13 LOBC and 21 LABC) received TP. Age, menopausal status and number of first/second degree relatives affected, Nottingham Prognostic Index (NPI) were closely comparable for both arms. MRM could be done in 62.2% (FEC) and 86.1% (TP) patients (p value 0.020). Post- NACT pathological T0 (ypT0) was achieved in 13.5% & 41.7% patients of FEC and TP arms, respectively (p value 0.007). Complete response (CR) and partial response (PR) were achieved in 13.5% and 43.2% (FEC arm) vs. 33.3% and 63.9% (TP arm); p value 0.001. mPFS was 13 months(FEC) vs. 17 months(TP) (p value 0.001). No significant difference in terms of severe hematological toxicities was found (21.6% Vs 22.2%, p=0.61) though neurological toxicities were slightly more common in TP arm.

**Conclusion:** Platin-taxane combination chemotherapy was proven promising over anthracycline-based combination chemotherapy in neo-adjuvant setting while treating TNBC of various stages in terms of efficacy considering tolerable toxicity profile.

*Keywords: TNBC; NACT; platin; anthracycline.*

## 1. INTRODUCTION

According to the nomenclature in Triple-negative breast cancer (TNBC) all three receptors i.e. estrogen receptor (ER), progesterone receptor (PR) and HER2 stain negative [1]. For this reason hormone therapy (HT) and HER2 targeted therapy remain ineffective in the course of entire treatment of TNBC. Standard cytotoxic chemotherapy regimens form the mainstay of treatment in TNBC. Further, as TNBC has higher propensity of visceral metastases, the median progression free survival after first line chemotherapy is twelve weeks only; while for second and third line these are nine weeks and four weeks, respectively. The survival (7-13 months) is also relatively shorter [2-4]. Hopefully, a number of published literature demonstrated that cytotoxic chemotherapy is beneficial in TNBC, especially in neoadjuvant setting a number of regimens have proved themselves effective. It is also evident that, rate of pathologic complete response (pCR) is significantly higher in TNBC than that in case of oestrogen receptor positive breast cancer following neoadjuvant chemotherapy (NACT), and pCR is directly associated with significantly better outcome [5,6]. Considering NACT a new horizon for exploration in TNBC this study was designed to comparatively analyse the response and survival between a platin-based and an anthracycline-based combination chemotherapy regimen. However, the comparison between Carboplatin plus Paclitaxel (TP) vs. 5FU plus Epirubicin plus Cyclophosphamide (FEC) was done not only in TNBC patients of large operable breast cancer (LOBC) and locally advanced breast cancer

(LABC) but also in selected early breast cancer (EBC) patients as NACT.

## 2. MATERIALS AND METHODS

### 2.1 Patients and Methods

In this single institutional retrospective study total 73 consecutive patients who got registered between January, 2014 and December, 2016 in the oncology out-patient department of R G Kar medical College and Hospital were included. After clinical evaluation including local and locoregional examination of bilateral breast and axillae a complete mammogram with proper BIRADS scoring was done. It was followed by a tru-cut biopsy report confirming the pathological diagnosis of invasive breast cancer. As fine needle aspiration cytology sample does not suffice to perform immunohistochemistry, tru-cut biopsy was mandatory. It was followed by an immunohistochemistry, negative for estrogen receptor, progesterone receptors and HER2. Ki 67 was not routinely done. Instead we considered Modified Nottingham Prognostic Index (NPI) Scoring to determine the grade of aggressiveness of the neoplasm. It was followed by complete metastatic work up including a chest X ray, a Contrast Enhanced Computed Tomography Scan of whole abdomen and a Magnetic Resonance Imaging of brain. Patients who are clinically, AJCC anatomic prognostic stage group IIB (T2N1, T3N0), IIIA (T2N2, T3N1, T3N2) and IIIB (T4N0, T4N2) were included. Significant baseline characteristics used for patient matching included history regarding age (<50 years vs. >50 years; no more than 3 years

apart), menopausal status (premenopausal vs. postmenopausal), number of relatives affected (1<sup>st</sup> degree vs. 2<sup>nd</sup> degree vs. no family history). BRCA 1 and BRCA 2 mutation analysis was not routinely done in our institution. Other minor factors like age at first child birth (no more than 2 years apart), duration of breast feeding (obtained from parity), month that patients received the treatment (no more than 6 months apart) were attempted to match afterwards. Patients who could not complete all 6 cycles of NACT due to grade 3 toxicities were excluded.

## 2.2 Treatment Protocol

After proper pre-chemotherapy work up including complete blood count, kidney function test, liver function test, diabetic profile, serology and cardiological fitness including echocardiography and electrocardiogram patient were distributed in two major groups for administration of NACT. The first group received 6 cycles of either Paclitaxel 175 mg/m<sup>2</sup> and Carboplatin at an Area Under Curve (AUC) 5 iv on day1, every 21 days followed by three subcutaneous dose of Granulocyte Colony Stimulating Factor (G-CSF) 300 mcg on day 2, day 3, day 4 according to our institutional primary prophylaxis protocol for the regimen to prevent neutropenia. Patients of the other arm received 5FU 500 mg/m<sup>2</sup>, Epirubicin 100 mg/m<sup>2</sup>, Cyclophosphamide 500 mg/m<sup>2</sup> iv on day1 followed by day 2 and day 3 dose of primary prophylaxis G-CSF. Primarily, a routine clinical examination for response assessment was done after 3 cycles. After 14 days following the completion of all 6 cycles of chemotherapy the patient was assessed for further radical intervention including modified radical mastectomy (MRM) and adjuvant Radiation Therapy (RT) with 50Gy in conventional fractionation. Those who could not be treated with curative intent after completion of NACT due to disease progression with distal metastasis (DM) were treated with palliative intent.

## 2.3 Response Assessment

Patients who underwent MRM were assessed by the histopathological examination of the specimen. Pathological T stage (pT) and pathological N stage (pN) were the main criteria to assess the downstaging reflecting the efficacy of either regimen. RECIST v1.1 criteria were used to determine progressive disease (PD), pathological complete response (pCR), partial response (PR) and static disease (SD). After completion of radiation therapy clinical

examination of bilateral breasts and axilla and a high resolution ultrasonography of ipsilateral chest flap, contralateral breast and bilateral axillae was done after 2 months. A chest X ray and a CECT whole abdomen was done 3-4 monthly. MRI brain was performed on the basis of presenting symptoms as and when required. median progression free survival (m PFS) and overall survival (OS) was assessed using Kaplan-Meier survival analysis over a median follow up of 40 months.

## 2.4 Statistical Analysis

SPSS statistical software version 17 (IBM Corp., Chicago, IL, USA) was used for data analysis. Quantitative data were presented by mean or median as appropriate, and qualitative data were presented as percentage. OS and PFS were analysed by the Kaplan-Meier method and compared between both groups by log rank test. The Cox proportional hazards model was used to adjust all prognostic factors. A 2-sided p-value <0.05 was considered statistically significant.

## 3. RESULTS

During the study period total 73 patients were identified and included. Only 5 (6.8%) patients with EBC were included as they were given NACT followed by MRM instead of upfront surgery. Overall LOBC and LABC cases were 24 (32.9%) and 44 (60.2%) respectively. Out of 37 patients who received FEC were stratified into 3 EBC, 11 LOBC and 23 LABC and out of 36 patients of TP arm 2, 13 and 21 were EBC, LOBC and LABC respectively. Distribution of cT and cN status is depicted in Table 1.

While the mean age for the entire cohort it was 52.16 years, mean age for the FEC group was 51.41 years (range 37-70 years) and for TP it was 52.94 years (range 38-66 years) (p value = 0.436). For both groups median age of first child birth was 23. 4 and 5 patients had affected first degree relatives while 7 and 6 patients had affected second degree relatives in the FEC and TP group, respectively. Factors like age of menarche and age of menopause and parity were also comparable. Modified Nottingham Prognostic Index (NPI) score was 2 for majority of patients i.e. 64.9% in FEC and 61.1% in TP arm.

After completion of 6 cycles of NACT in both the arm radical treatment including MRM and post mastectomy RT could be given with curative

intent in 23 (62.2%) patients in the FEC arm and 31 (86.1%) patients in the TP arm. P value was 0.02 which was significant statistically. Remaining 19 patients of the entire cohort were treated with palliative intent afterwards.

Assessment of ypT/ ycT status revealed greater response in the TP arm with a significant P value (Table 2), though for ypN/ ycN the P-value was not significant statistically.

pCR was evident in 5 (13.5%) patients and 12 (33.3%) patients and partial response occurred in 16 (43.2%) patients and 33 (63.9%) patients for FEC and TP regimens, respectively carrying a significant P value 0.001.

For the entire cohort mPFS was 15 months. Median PFS was 13 months (95% confidence interval: lower bound 9.02; upper bound 16.97) for FEC arm and 17 months (95% confidence interval: lower bound 12.10; upper bound 21.90) for TP arm. Log rank p value was 0.001. Kaplan-meier survival curve significantly showed the survival difference (Fig. 1).

Site of disease progression was visceral in majority of patients accounting for 73.0% in FEC arm and 58.3% in TP arm. Bone metastases occurred in 10.8% (FEC) and 11.1% (TP) patients. This results clearly nodded for the

propensity of TNBC for visceral metastases. Other disease progression events were locoregional.

For the entire cohort median OS was 25 months. Median OS was 21 months (95% confidence interval: lower bound 17.60; upper bound 24.39) for FEC arm and 29 months (95% confidence interval: lower bound 23.12; upper bound 34.88) for TP arm. Log rank p value was 0.009. Kaplan-meier survival curve significantly showed the survival difference (Fig. 2).

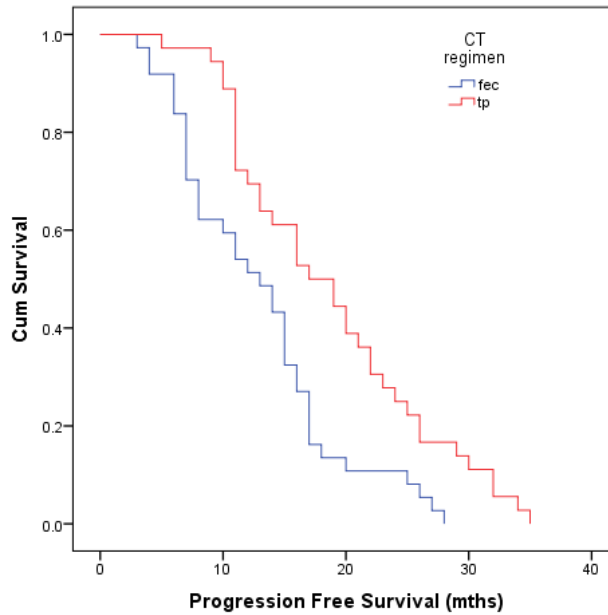
Hematotoxicity in the form of decreased absolute neutrophil count (<1500/cumm) was seen in 21.6% patients of FEC arm and 22.2% patients of TP arm. According to our institutional protocol secondary G-CSF prophylaxis sufficed to combat neutropenia. Along with proper intravenous premedication, oral Aprepitant (125 mg) was given an hour prior to the administration of FEC cycles on day 1 which was followed by 80 mg on day 2 and day 3. In spite of this, slightly higher occurrence of emesis was evident in FEC arm (13.5%) in comparison with TP arm (8.33%). Hypersensitivity, revealed in only one patient following administration of Paclitaxel in first cycle managed accordingly. No significant taxane neurotoxicity came into scene except mild tingling sensation and apparent hypoesthesia in finger tips in three patients of TP arm.

**Table 1. Distribution of cT/cN status at baseline in FEC and TP arm**

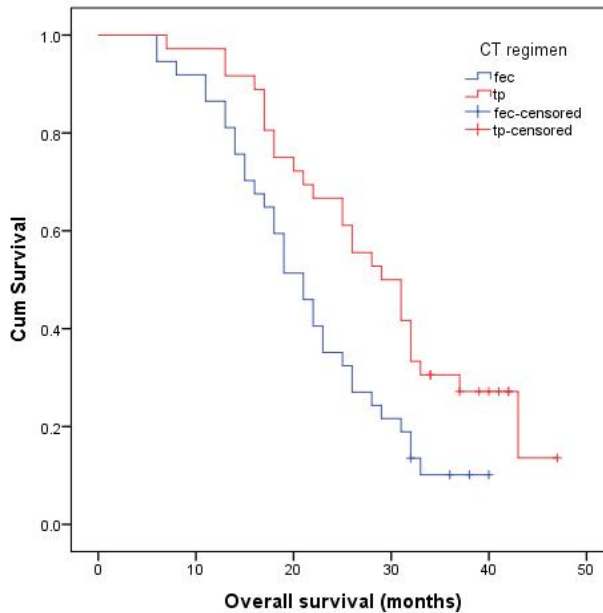
		CT Regimen				P value
		FEC		TP		
		Count	Column N %	Count	Column N %	
cT	2	8	21.6%	5	13.9%	0.770
	3	14	37.8%	18	50.0%	
	4a	5	13.5%	4	11.1%	
	4b	9	24.3%	7	19.4%	
	4c	1	2.7%	1	2.8%	
	4d	0	0.0%	1	2.8%	
cN	0	9	24.3%	11	30.6%	0.424
	1	21	56.8%	15	41.7%	
	2	7	18.9%	10	27.8%	

**Table 2. ypT/ycT and ypN/ycN status in FEC and TP arm**

		NACT regimen				P value
		FEC		TP		
		Count	Column N %	Count	Column N %	
ypT/ycT	t0	5	13.5%	15	41.7%	0.007
	t1	5	13.5%	5	13.9%	
	t2	15	40.5%	14	38.9%	
	t3	12	32.4%	2	5.6%	
ypN/ycN	n0	14	37.8%	23	63.9%	0.075
	n1	20	54.1%	12	33.3%	
	n2	3	8.1%	1	2.8%	



**Fig. 1. Progression free survival for FEC vs TP**



**Fig. 2. Overall survival for FEC vs TP**

At the end of the study out of total 13 living patients 4 (10.8%) belonged to the FEC arm and 9 (25.0) patients belonged to the TP arm.

**4. DISCUSSION**

In 2005, Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis

clearly showed the benefit of polychemotherapy in ER-negative breast cancer [7]. Though definite data on HER-2 neu negativity is a major limitation of this decade old meta-analysis, yet the fact that cytotoxic chemotherapy is substantially beneficial in TNBC was re-established. Data of 1,118 patients treated in MD Anderson Cancer Center between 1985 and

2004 was analysed to compare the response to NACT in TNBC vs. non-TNBC [5]. While 23% TNBC patient were detected with pCR, the same was evident in 11% of non-TNBC arm which was even less than half. This largely conducted study also suggested that non-TNBC group was superior than the TNBC group not only in term of 3-year progression free survival (76% in non-TNBC vs 63% in TNBC), but also in term of 3 year overall survival (89% in non-TNBC vs 74% in TNBC). NSABP B-27 trial including 2411 patients was a milestone in establishing the role of taxane in neoadjuvant setting. In this three armed robust randomised study arm-A patients received 4 cycles of standard Doxorubicin-Cyclophosphamide (AC) every three weeks followed by surgery. Arm-B received four more cycles of three weekly Docetaxel (i.e. AC X 4 → T X 4 ) before surgery and for the C-arm surgery was sandwiched between four cycles of AC and four cycles of T. B-arm i.e. AC→T→surgery arm had 26.1% pCR rate which was almost double in comparison with arm-A (12.9% pCR) and arm-C (14.4% pCR) [8]. A phase II study including TNBC of stage group II and III was conducted to evaluate the role of four cycles of single agent Inj. Cisplatin 75 mg/m<sup>2</sup> IV. Miller-Payne score was 4 or 5 in 36% patients indicating complete / near complete response. The pCR rate was 22% which was promising too [9,10]. Another study following the previous one in which Inj. Bevacizumab was added to Inj. Cisplatin in neoadjuvant setting in 51 TNBC patients concluded in 16% pCR and 37% Miller-Payne score 4-5 [11]. However, the fact that platin may have an active role in the treatment of TNBC was re-established by dint of these two studies. Taxane-platin regimen (Paclitaxel plus Cisplatin) was assessed in a phase II study published in 2004 for LABC patients regardless to ER, PR, and HER2 status which resulted in 28% CR and 63% PR [12]. While in a study a weekly regimen consisting Inj. Paclitaxel 120 mg/m<sup>2</sup> IV plus Inj. Cisplatin 30 mg/m<sup>2</sup> IV plus Inj. Epirubicin 50mg/m<sup>2</sup> IV was administered in 74 TNBC patients for eight weeks with appropriate G-CSF support on day 3, day 4 and day 5, a magically higher pCR rate of 65% became evident [13].

Apart from the crowd of studies which strongly established the role of anthracycline in TNBC there is an analysis from the MA 5 published in 2009 in which CEF regimen (cyclophosphamide plus epirubicin plus 5-fluoruracil) was proved inferior to CMF regimen (cyclophosphamide plus methotrexate plus 5-fluoruracil) in term of 5-year overall survival (71% for CMF and 51% for

CEF) for TNBC patients. However this negative study was performed in adjuvant setting and in all other sub-groups CEF was superior [14].

Lastly, it can be said that though TNBC is the most aggressive molecular variety of breast cancer, yet a major subset of it is highly sensitive to cytotoxic chemotherapy. Foulkes et al. in 2010 felt the necessity of continuing research on different regimens in different settings for this aggressive entity to establish an optimum regimen [15]. To the best of our knowledge, our study is the first Indian trial to compare an anthracycline based regimen with a platinum-taxane based one in TNBC patients. It is prominent from the result demonstrating the 33.3% pCR rate in the TP arm while compared to the 13.5% pCR in the FEC arm that platinum-salt has higher cytotoxic efficacy. Further, while ypT status of both arms was considered the significant p value (0.007) consolidated the same fact. A progression free survival benefit of 4 months was promising too.

## 5. CONCLUSION

In a nutshell it can be said that though we achieved a significant response with the TP regimen but the mPFS revealed that the benefit was short lasting. However, considering the fact that the primary objective of the neoadjuvant therapy is to achieve downstaging or more clearly pCR, our study was a step to establish the platin based cytotoxic chemotherapy as an optimal regimen to be used in neoadjuvant setting in Indian TNBC patients with acceptable toxicities.

## CONSENT

All authors declare that written informed consent was obtained from each patient (or other approved relative).

## ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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