International Journal of Advances in Medicine
Anand AS et al. Int J Adv Med. 2016 Feb;3(1):5-10
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20151251

Research Article

Primary systemic chemotherapy in locally advanced breast cancer-taxane versus non-taxane combination chemotherapy schedule

Aravindh S. Anand*, Biju U. Francis

Department of Radiotherapy & Oncology, Government Medical College, Thiruvananthapuram, Kerala, India

Received: 01 November 2015
Accepted: 23 November 2015

***Correspondence:**
Dr. Aravindh S. Anand,
E-mail: anandrt2006@yahoo.com

ABSTRACT

Background: Primary systemic chemotherapy (PST) forms a pivotal role in the management of primarily inoperable locally advanced breast cancer (LABC). Studies have revealed that complete pathologic response (pCR) is a surrogate marker of survival of LABC patients. In this study we aim to compare two chemotherapy regimens TAC vs. FAC/FEC. Endpoints are pCR and toxicity.
Methods: 130 primarily inoperable LABC patients who received PST with either taxane containing chemotherapy TAC (Docetaxe l75 mg/m^2, Adriamycin 50 mg/m^2, Cyclophosphamide 500 mg/m^2) or non-taxane chemotherapy FAC (5-Flurouracil 500 mg/m^2, Adriamycin 50 mg/m^2, Cyclophosphamide 500 mg/m^2)/FEC (5-Flurouracil 500 mg/m^2, Epirubicin 100 mg/m^2, Cyclophosphamide 500 mg/m^2) were prospectively observed and studied as two treatment arms- Taxane arm (70 patients) or Non-taxane arm (60 patients). Patients in each arm received maximum 6 cycles of taxane or non-taxane chemotherapy. Tumor response & toxicity was assessed.
Results: 25.7% patients in taxane arm and 10% patients in non-taxane arm had complete pathological response (p=0.014). 90% in taxane arm and 86.7% in non-taxane arm became operable after PST (p=0.564). Grade 3 or 4 neutropenia was seen in 45.7% and 3.3% in Taxane and non-Taxane arm respectively (p=0.000). All patients completed the planned treatment in spite of the higher incidence of Grade 3/4 neutropenia in the docetaxel arm.
Conclusions: TAC has significantly better complete pathologic response with tolerable toxicity. Hence in Indian LABC patients as well, taxane containing chemotherapy in the primary setting is the better option. Longer follow up of this study may confirm whether the better pathologic response may translate to better survival.

Keywords: Locally advanced breast cancer, Tumor response, Taxane

INTRODUCTION

Breast cancer is the most common cancer in women worldwide and in the urban population in India. In India 1 in 28 women develop breast cancer during her life time. This is higher in urban areas where it is 1 in 22 and in rural areas it is 1 in 60 women, which is relatively low.[1] In Kerala state despite the good health indicators, breast cancer is a public health problem and annual incidence is 14.9/100,000 population.[2]

Last decade witnessed a dramatic change in the understanding of biology and heterogeneity of breast cancer. This advanced knowledge in the biology paved the path for development of new therapies and treatment strategies with emphasis on tailored therapy. Locally advanced breast cancer (LABC) constitutes more than 50% of breast cancer at diagnosis in developing countries like India. Primary systemic chemotherapy (PST) followed by modified radical mastectomy with axillary clearance, local radiation treatment and hormonal treatment is the standard accepted treatment for this

group of patients. This multi-modality treatment approach can provide improved control of loco-regional and systemic disease. But the optimal treatment of this group is yet to be defined due to the heterogeneity. Regarding the primary systemic chemotherapy regimen, the most common anthracycline chemotherapy schedules are FAC (Fluracil, Adriamycin, Cyclophosphamide) or FEC (Fluracil, Epirubicin, Cyclophosphamide) while most common taxane containing regimens are TAC (Docetaxel, Adriamycin, Cyclophosphamide) or AT (Adriamycin, Docetaxel). Preoperative chemotherapy regimens which has high clinical response rate include anthracycline containing regimen (Adriamycin & Cyclophosphamide) followed by a taxane (Paclitaxel or Docetaxel) or vice versa. Some of the recent data indicate that the pathologic complete response rate is enhanced by dose dense regimens. Neoadjuvant chemotherapy has the same impact on the disease free and overall survival as adjuvant chemotherapy. It has shown a complete clinical response rates ranging from 20% to 53% and partial response rate ranging from 37% to 50%, with a total response rate of 80 to 90%. Pathologic complete response rate in the primary breast and axillary lymph node has significantly improved the disease free survival compared with those who have less than pCR.[3]

Pathologic complete response to neoadjuvant chemotherapy has become an intermediate surrogate marker for disease free and overall survival. Therefore factors predicting a complete pathologic response have become the focus of a number of clinical trials. The impact of systemic chemotherapy on local control has received increasing attention with the recent meta-analysis of randomized trials demonstrating that one breast cancer death will be avoided for every four local recurrences prevented.

In India where the incidence of LABC is high and tumor biology is high, studies comparing taxane vs. Non-taxane chemotherapy in neo-adjuvant setting is sparse. In this study our primary objective is assessment of PCR and secondary objectives were complete clinical response, operability, toxicity and tolerability.

METHODS

This study is a prospective observational cohort study of 130 LABC patients who were primarily inoperable and received primary systemic chemotherapy with either a taxane or non-taxane containing combination chemotherapy from January 2013 to January 2014 in our institution. The inclusion criteria was female patients less than 75yrs, primarily inoperable LABC, histopathological evidence of invasive cancer by core biopsy, normal bone marrow reserve, renal, liver and cardiac function. Patients who were unwilling for the study, those with previous treatment for any other malignancies and with any contraindication for anthracycline were excluded from the study.

Consecutive patients fulfilling the inclusion criteria and willing for the study were enrolled after written informed consent. They were grouped into two arms- Taxane and non-Taxane arms. Taxane arm patients received TAC (Docetaxel 75 mg/m^2, Doxorubicin 50 mg/m^2, Cyclophosphamide 500 mg/m^2) three weekly up to 6 cycles. Non Taxane chemotherapy arm received either FAC (Fluracil 500 mg/m^2, Adriamycin 50 mg/m^2, Cyclophosphamide 500 mg/m^2) or FEC (Fluracil 500 mg/m^2, Epirubicin 100 mg/m^2, Cyclophosphamide 500 mg/m^2) three weekly up to 6 cycles. A detailed elucidation of history & clinical examination was done prior to the start of treatment. Patients had cardiology evaluation including an ECHO scan, for the fitness for the use of anthracycline. Clinical examination and toxicity assessment was done after each chemotherapy cycle. Clinical response was assessed as per RECIST criteria[4] and toxicity as per NCI toxicity criteria.[5] Patients who became operable after 6 cycles of chemotherapy were referred for surgery in our institution itself. Those patients who remained inoperable were given local radiation treatment to intact breast & axilla. HER-2neu receptor positive patients were offered adjuvant trastuzumab with a loading dose of 4 mg/kg followed by weekly 2 mg/kg for at least 9 weeks and up to a period of 1 year. Patients who underwent mastectomy were given radiation to chest wall and drainage areas to a dose of 50Gy/25 fractions over a period of 5 weeks. Those patients who were endocrine responsive (estrogen or/and progesterone receptor positive) were offered hormonal treatment as per standard guidelines.

RESULTS

Table 1: Distribution based on clinical tumor stage.

cT Stage	FAC		TAC		Total	
	No.	%	No.	%	No.	%
cT3	28	46.7	30	42.9	58	44.6
cT4a	2	3.3	0	0	2	1.5
cT4b	26	43.3	34	48.6	60	46.2
cT4c	4	6.7	6	8.6	10	7.7
Total	60	100	70	100	130	100

$\chi 2$ =2.783; df =3; p=0.426

Table 2: Distribution based on clinical nodal stage.

cT Stage	FAC		TAC		Total	
	No.	%	No.	%	No.	%
N1	30	50	36	51.4	66	50.8
N2	14	23.3	12	17.1	26	20
N3	10	16.7	16	22.9	26	20
N0	6	10	6	8.6	12	9.2
Total	60	100	70	100	130	100

$\chi 2$ =1.323; df =3; p=0.724

Table 3: Distribution based on pathological complete response.

Pathological response	FAC		TAC		Total	
	No.	%	No.	%	No.	%
Complete pCR	6	10	18	25.7	24	18.5
No complete pCR	50	83.3	42	60	92	70.8
Cannot be assessed	4	6.7	10	14.3	14	10.8
Total	60	100	70	100	130	100

$\chi 2$ =8.548; p=0.014

Table 4: Distribution of patients based on neutropenia.

cT Stage	FAC		TAC		Total	
	No.	%	No.	%	No.	%
Grade 0	42	70	26	37.1	68	52.3
Grade 1	10	16.7	4	5.7	14	10.8
Grade 2	6	10	8	11.4	14	10.8
Grade 3	2	3.3	22	31.4	24	18.5
Grade 4	0	0	10	14.3	10	7.7
Total	60	100	70	100	130	100

$\chi 2$ =32.713; df =4; p=0.000

Table 4: Distribution of patients based on cardiac toxicity.

Cardiac toxicity	FAC		TAC		Total	
Dysarrthymia	Grade 0	66.7	57.1	61.5	1.238	0.266
	Grade 1	33.3	42.9	38.5		
Ischemia	Grade 2	93.3	100	96.9	4.815	0.028
	Grade 3	6.7	0	3.1		
LV dysfunction	Grade 4	63.3	60	61.5	0.152	0.697
	60	36.7	40	38.5		

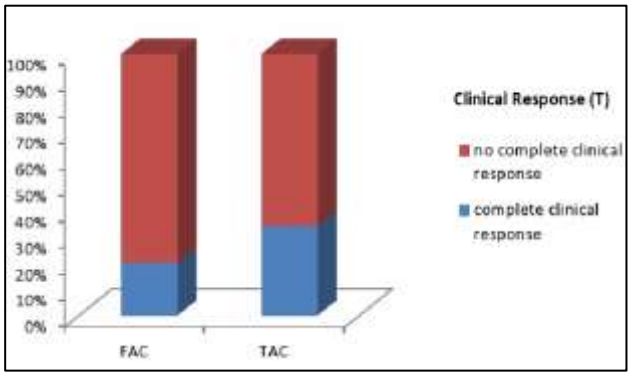

Figure 1: Distribution based on clinical tumour response.

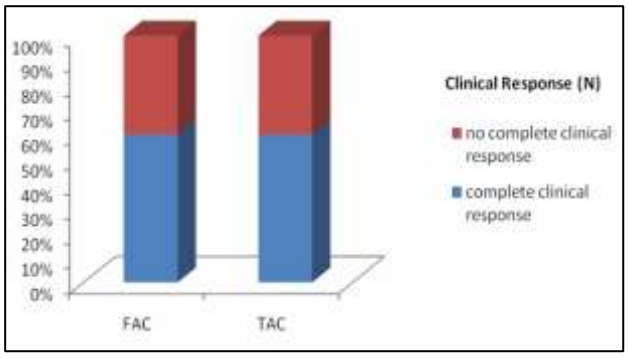

Figure 2: Distribution based on clinical nodal response.

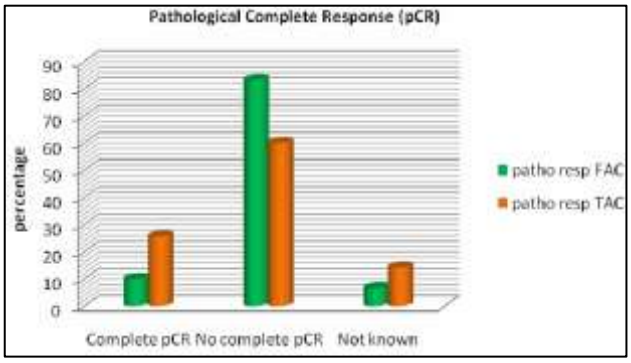

Figure 3: Distribution based on pathological complete response.

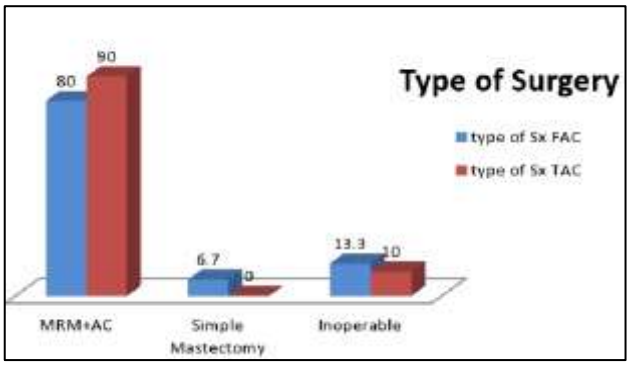

Figure 4: Distribution based on type of surgery perfomed.

With regard to the clinical tumour response to PST (Figure1), 35.7% of patients in taxane arm and 18.3% in non-taxane arm had complete clinical tumour response (p= 0.070). 60% of patients had complete nodal response (Figure 2) in both taxane and non-taxane arms. 25.7% patients in the taxane arm and 10% patients in non-taxane arm had complete pathological response (pCR) (Table 3 & Figure 3). 90% in the taxane arm and 86.7% in the non-taxane arm became operable (Figure 4) after PST. (p=0.564). 90% and 80% in the taxane and non-taxane arm respectively underwent modified radical mastectomy plus axillary clearance (MRM+AC). 6.7% patients in non-taxane arm underwent simple mastectomy. In taxane arm, all the patients who became operable underwent MRM+AC.

Grade 0 & 1 anaemia was almost similar in both the study group. It was 97.2% in taxane arm and 96.7% in non-taxane arm. Grade 3 or 4 neutropenia was seen in 45.7% and 3.3% in taxane and non-taxane arm respectively (Table 4). 16.7% patients in non-taxane and 37.1% patients in taxane developed grade 1 thrombocytopenia. The percentage of patients who developed grade 2 thrombocytopenia in taxane group was 17.1% whereas in the non taxane it was only 3.3%. (p=0.000).

In the taxane group, incidence of nausea were 57.1% grade 1, 31.4% grade 2 and 11.4% grade 3 while in the non-taxane group it was 10% grade1, 80% grade 2 and 10% grade 3. Incidence of vomiting in taxane arm was grade1 in 65.7%, grade 2 in 28.6% and grade 3 in 5.7%. Whereas in the non-taxane group it was 6.7% grade1, 80% grade 2 and 13.3% grade 3. With regard to chemotherapy induced diarrhoea in taxane group it was 51.4% grade 3, 40% grade 2, 8.6% grade 1 and none with grade 0. In the non-taxane group diarrhoea was grade 0 in 33.3%, grade1in 56.7%, grade 2 in10% and grade 3 in none of the patients. Stomatitis was grade 0 in 14.3%, grade 1 in 37.1% and grade 2 in 48.6% in taxane arm. In non-taxane group 60% of patients had grade 0 and remaining 40% had grade 0. None of the patients had grade 2 stomatitis.

There is statistically significant difference between two treatment groups with respect to ischemia (Table 5). In the non-taxane regimen group, 6.7% of patients developed grade1 ischemia and none of the patients in taxane developed ischemia. In the non taxane group, 33.3% of patients were having grade1dysarrthymia. In the taxane group, 42.9% of patients were having grade 1 dysarrthymia.

There is no statistically significant difference between two treatment groups with respect sensory and motor neurological toxicity. In the taxane regimen group, 28.6% of patients were having grade 1 sensory neurological toxicity, 8.6% of patients were having grade 2 toxicity. In the non taxane group, the Grade 1&2 sensory neuro-toxicity was 13.3% & 3.3% respectively. In the taxane arm, 25.7% of patients were having grade 1motor toxicity & 2.9% of patients were having grade 2 motor toxicity. In the non-taxane arm it was 16.7% & 6.7% respectively. No statistically significant differences exist between two treatment groups with respect to changes in the liver enzymes and bilirubin.

Most common site for metastasis within this limited period of study was bone followed by brain. Out of the 16 patients (12.3%) who developed metastasis, 8 (11.4%) were in Taxane group and 8 (13.3%) were in non-Taxane group.

DISCUSSION

Patients with LABC do poorly when treated by loco regional therapy alone. Such therapy favourably enhances loco regional control, but most relapses are due to the development of distant metastases. Primary systemic therapy regimens have shown to have a favourable effect on the outcome of patients with LABC with regard to down staging the disease and increasing the operability. This study conducted in our institution compared the efficacy and safety profile of two commonly used chemotherapy regimens in the management of locally advanced breast cancer. The study was aimed to evaluate the role of taxane in the management of LABC in the Indian scenario.

In this study 51% patients were in N1 status at the time of presentation and 20% were in N2 stage. 56.2% patients were ER/PR positive and 43.8% were negative. In an Indian study by Desai SB et al the percentage of tumour with ER positivity was 32.6%. In a study by Tanuja et al which is a large Indian study of 11,780 breast cancers, the hormone positivity is 53.9% which is almost same as our finding.[7,8] But the overall receptor expression is less in Indian population when compared to western population. This may be due to the fact that majority of the patients present in advanced stage and the grade of the tumors are high.

In this study, a total of 18.5% had pathological complete response. In the taxane arm 25.7% patients had pathological complete response whereas in the non-taxane arm, it is only 10%. There is statistically significant difference between the two treatment groups with regard to pathologic response. Our study clearly proves that In Indian patients also, addition of taxanes improves the pathological complete response. Our result correlates with several other studies and stress the fact that addition of taxanes in the neoadjuvant setting improves the outcomes in locally advanced breast cancer patients.[9-17]

In our study, 27.7% patients had complete clinical tumour response. This tumour response that we achieved in our study is similar to the results in some of the studies in the literature. At the same time it is even higher than that seen in several other studies [18]. In FAC arm 18.3% had

complete clinical tumour response and in TAC arm 35.7% had complete clinical tumour response even though the difference not statistically significant. 60% of patients had complete clinical nodal response and it was the same in both the groups. In this study, in total 88.5% patients became clinically operable after the primary systemic therapy. 90% of patients in TAC and 86.7% patients in FAC arm became operable. Thus with regard to debulking the tumour and making it operable both chemotherapy regimen are somewhat similar.

With respect to bone marrow toxicity, the incidence of neutropenia Grade 3 & 4 together is 45.7% in the TAC arm whereas it is only 3.3% in non-Taxane arm. Prophylactic G-CSF and strict monitoring of the patient is advisable in the TAC arm. Grade 3 or 4 neutropenia even though it was significantly higher in the docetaxel containing arm, there was no treatment related deaths and all patients were treated with standard neutropenia guidelines. All patients completed the planned treatment in spite of the higher incidence of Grade 3/4 neutropenia in the docetaxel arm.

Our study has some limitations. Even though it is a prospective study, it is not a randomized study. But still, from the available data from this study and the data from several randomized trials it is better to advise a taxane containing combination chemotherapy in locally advanced breast cancer for better tumour response. In Indian patients this has more implications as patients present at advanced stage and the tumour biology is more aggressive due to low expression of hormone receptors and high tumour grade. Our study need to be followed up for longer period to confirm whether this clinical and pathological tumour response will be translated to better survival.

CONCLUSIONS

In developing countries like India, where there is no routine screening of breast cancer the incidence of locally advanced breast cancer is high and a clinical problem. So any study in improving the outcome of this subset of patients must be of high priority for the benefit of the society. Both TAC and FAC/FEC are excellent combination chemotherapy regimen for down staging LABC and making it operable. But TAC has significantly better complete pathologic response and also well tolerated in spite of increased bone marrow toxicity. Hence taxane containing chemotherapy in the primary setting is a better option for Indian LABC patients as well. Longer follow up of this study may confirm whether the better pathologic response may translate to better survival.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Information by type of cancer, Tata Memorial Hospital. Available at www.tmc.gov.in, 2014.
2. National Center for Biotechnology Information; www.ncbi.nlm.nih.gov.
3. Symmans WF, Peintinger F, Hatzis C. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy J Clin Oncol. 2007;25:4414-22.
4. 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) European Journal of Cancer. Eur J Cancer. 2009;45(2):228-47.
5. NCI Common Toxicity Criteria version 2.
6. Bear HD, Anderson S, Brown A. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2003;21:4165-74.
7. Desai SB, Moonim MT, Gill AK, Punia RS, Naresh KN, Chinoy RF. Hormone receptor status of breast cancer in India: A study of 798 tumors. Breast. 2000;9:267-70.
8. Shet T, Agrawal A, Nadkarni M, Palkar M, Havaldar R, Parmar V, et al. Hormone receptors over the last 8 years in a cancer referral center in India: What was and what is? Indian J Pathol Microbiol. 2009;52:171-4.
9. Chen XS, Nie XQ, Chen CM, Wu JY, Wu J, Lu JS. Weekly paclitaxel plus carboplatin is an effective non anthracycline-containing regimen as neoadjuvant chemotherapy for breast cancer. Ann Oncol. 2010;21:961-7.
10. Von Minckwitz G, Costa SD, Eiermann W, Blohmer JU, Tulusan AH, Jackisch C, et al. Maximized reduction of primary breast tumor size using preoperative chemotherapy with doxorubicin and docetaxel. J Clin Oncol. 1999;17:1999-2005.
11. Miller KD, McCaskill-Stevens W, Sisk J, Loesch DM, Monaco F, Seshadri R, et al. Combination versus sequential doxorubicin and docetaxel as primary chemotherapy for breast cancer: A randomized pilot trial of the Hoosier Oncology Group. J Clin Oncol. 1999;17:3033-7.
12. Malhotra V, Dorr VJ, Lyss AP, Anderson CM, Westgate S, Reynolds M, et al. Neoadjuvant and adjuvant chemotherapy (CT) with doxorubicin and docetaxel (DD) with surgery and radiation in locally advanced breast cancer. Proc Am Soc Clin Oncol. 1999;2:b6.
13. Valero V, Esteva FJ, Sahin AA, Booser DJ, Strom EA, Esparza-Guerra LT, et al. Phase II trial of neoadjuvant chemotherapy with docetaxel and doxorubicin, surgery, adjuvant CMF, and radiotherapy ± tamoxifen in locally advanced breast cancer. Breast Cancer Res Treat. 2000;64:69.

14. Bouzid K, Vinholes J, Salas F, Mickiewicz E, Valdivia S, Ostapenko V, et al. A Phase III trial of Taxotere and doxorubicin (AT) vs. 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) in patients with unresectable locally advanced breast cancer: An interim analysis. Eur J Cancer. 2010;37:s167.
15. von Minckwitz G, Costa SD, Raab G, Blohmer JU, Eidtmann H, Hilfrich J, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast. A randomized, controlled, open phase IIb study. J Clin Oncol. 2001;19:3506-15.
16. Bines J, Vinholes J, Del Giglio A, Vasconcelos A, Cabral C, Gusmao C, et al. Neo-adjuvant chemotherapy with weekly docetaxel (taxotere) in poor prognosis locally-advanced breast cancer (LABC). Breast Cancer Res Treat. 2002;76:s54.
17. Andrade JM, Carrara HH, Pimentel FF, Marana HR, Macchetti AH, Mouro LR, et al. Taxane-based chemotherapy enhances response to neoadjuvant treatment for stage II and III breast cancer. Med Oncol, 2010.
18. Omidvari S, Hosseini S, Ashouri Y, Tahmasebi S, Talei A, Nasrolahi H, et al. Comparison of Docetaxel, Doxorubicin and Cyclophosphamide (TAC) with 5-Fluorouracil, Doxorubicin and Cyclophosphamide (FAC) Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer: A Phase III Clinical Trial Middle East Journal of Cancer. 2011;2(2):51-8.

Cite this article as: Anand AS, Francis BU. Primary systemic chemotherapy in locally advanced breast cancer- taxane vs. non-taxane combination chemotherapy schedule. Int J Adv Med 2016;3:5-10.