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Study to Compare TAC versus FAC Regimen as Neoadjuvant Chemotherapy in Locally Advanced Breast Cancers

Authors
Sangita Narain[1], Smiti Narain[2], Varun Tiwari[3], Tanmay Prasad[4]
[1]Asst. Prof, Gynaecological Oncology, Dept of Radiotherapy, PMCH
[2]Asst. Prof, Dept of Community Medicine, Hi-Tech Medical College, Bhubaneswar
[3]Resident, Department of General Surgery, RRMCH
[4]MCh Resident, Department of Plastic Surgery, RRMCH

Abstract
Background and Objectives: *Neoadjuvant chemotherapy is used to downstage the tumours in LABC making it amenable to resection. Docetaxel, doxorubicin and cyclophosphamide (TAC) and 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) are used for Induction chemotherapy. The present study was done to compare the clinical and pathologic response of the two regimens.*
Material and Methods: *The study was performed in PMCH, Patna over a period of two years from July 2010 to June 2012 and then followed up for a period of five years in 126 patients randomized in two groups of TAC and FAC arms after which they all underwent a modified radical mastectomy. A follow up was done to study and compare the clinical response and toxicity in the two groups.*
Results: *Most common hematologic toxicity in both groups was neutropenia (33.87% and 23.43% in TAC and FAC arm respectively). TAC arm had better Disease-Free Survival (DFS) than FAC arm (64.28% vs 56.60% in stage IIIA in TAC and FAC arm respectively and 52.94% vs 44.11% in stage IIIB LABC in TAC and FAC arm respectively) at 5 years follow up.*
Conclusion: *TAC regimen used for neoadjuvant chemotherapy for locally advanced breast cancers has a better disease-free survival with lesser systemic toxicity as compared to FAC regimen.*
Keywords: *TAC regimen, FAC regimen, Neoadjuvant chemotherapy, LABC.*

Introduction

Breast cancer is the most common female cancer in with an increasing incidence. Although a screening mammography can detect a high proportion of early breast cancers, locally advanced breast cancer remains a major health problem in women, particularly in developing countries. Despite the progress in the treatment of these patients, the outcome and prognosis are poor [(1)].

Currently, all patients with locally advanced breast cancer is considered for neoadjuvant treatment[(2,3)]. Neoadjuvant chemotherapy was initially used for patients with inoperable breast cancer. This treatment approach has also made breast-conserving surgery a possibility. It has been shown that complete pathologic response is a one of the strong predictors of the efficacy of neoadjuvant therapy. In addition, for younger patients, few studies have suggested that a combined taxane and anthracyclin-based

chemotherapy regimen is better than either of them being used alone.[4]

Aim and Objectives

The aim of the present study was to compare the rates of complete clinical and pathologic response of docetaxel, doxorubicin and cyclophosphamide (TAC) vs. 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) as neoadjuvant chemotherapy in women with locally advanced breast cancer.

Material and Methods

The study was performed in Patna Medical College and Hospital which is a tertiary care hospital. Patients were selected over a period of two years from July 2010 to June 2012 and then followed up for a period of five years.

During the period, total number of breast cancer patients registered were 270. The total number of LABC patients were 221, out of which 162 patients were randomly selected for the present study, 36 patients were lost to follow up, thus 126 patients being the total number who completed the study and follow up. All patients with palpable breast masses were referred for neoadjuvant chemotherapy after taking an informed consent for the study.

A fine needle aspiration biopsy was performed for diagnosis and histopathology. The patients were assigned according to a random number table to receive either FAC or TAC neoadjuvant chemotherapy. The purpose of the study, the potential advantages of neoadjuvant treatment, and the risks and benefits of participation in the study were explained in detail to the patients. Chemotherapy-induced adverse effects such as hematologic suppression, nausea, vomiting, hair loss and nail changes etc were discussed with the patients.

Inclusion Criteria

1. Age 18–75 years
2. Previously untreated female patients having histopathologically documented case of ductal carcinoma of breast and HPE for Estrogen receptor/ Progesterone receptor status.
3. LABC cases of stage IIIA and IIIB, unilateral affected breast.
4. The patient with Karnofsky performance status ≥70
5. Normal or acceptable bone marrow, hepatic, cardiovascular and renal function tests, i.e., hemoglobin >10 g/dL, neutrophil count >1.5×109/L, platelet count >100×109/L, creatinine <2 mg/dL, bilirubin <2 mg/dL, alanine aminotransferase and aspartate aminotransferase <1.5× the upper normal limit, and alkaline phosphatase <1.5× the upper normal limit. Work-up for exclusion of metastasis consisted of chest X-ray, abdominal and pelvic ultrasonography and whole-body bone scintigraphy.

Exclusion Criteria

- The exclusion criteria were male breast cancer patients, patient refusal to consent, previous excisional biopsy, and comorbid medical conditions (heart disease, uncontrolled diabetes mellitus, psychiatric disease, and liver or kidney failure or insufficiency).
- In addition, those patients were excluded who had previously received radiotherapy, hormone therapy or chemotherapy with any agent and those with evidence of metastases or Stage IV Carcinoma Breast.

Procedure

Complete physical examination focused on evaluation of the breast and axillary lymph nodes including bi-dimensional tumour measurement (by callipers), detection of differences in breast sizes, skin thickness and warmth. Patients underwent assessments before intervention and prior to each cycle of chemotherapy. Tumour diameter was assessed by sonography before the first and after the sixth chemotherapy cycle. Patients underwent laboratory investigations, pre-

anaesthetic fitness for surgery and radiological investigations.

Chemotherapy consisted of six cycles of either FAC (5 fluorouracil 500 mg/m2, doxorubicin 50 mg/m2 and cyclophosphamide 500 mg/m2) or TAC (docetaxel 75 mg/m2, doxorubicin 50 mg/m2 and cyclophosphamide 500 mg/m2) administered every three weeks (Table 1). In the TAC arm, filgrastim [recombinant human granulocyte colony stimulating factor (G-CSF); 5 µg/kg] was prescribed for hematologic support during the fifth to ninth days after the completion of each cycle. All the patients subsequently underwent modified radical mastectomy after the last cycle of neoadjuvant chemotherapy.

Treatment related side effects such as myelosuppression, nausea and vomiting were managed according to the National Comprehensive Cancer Network (NCCN) protocols[5]. None of the patients had any treatment modifications (e.g., delay, dose reduction or both).

The outcomes were compared between treatments arms according to the longest tumour diameter measured after each cycle of chemotherapy. The last measurement was done after the sixth cycle of chemotherapy. Tumour response was assessed as follows: complete response was the complete disappearance of all assessable breast lesions by physical exam. Partial response was a reduction of more than 30% in the sum of the longest diameters of all measurable breast tumours compared to baseline; stable disease was a reduction of less than 30% or an increase of less than 20% in the sum of the longest diameters of all measurable tumours. Progressive disease was defined as an increase of more than 20% in the longest diameters of the original measurable tumours or the appearance of a new lesion. Toxicity was assessed according to the EORTC/RTOG criteria after each cycle of chemotherapy. The primary endpoints of the study were the rates of complete clinical and pathologic response, and a secondary endpoint was toxicity [6,7].

Table 1: TAC and FAC arm regimen with the doses used and duration of chemotherapy with the number of patients studied.

Study Design Arm	Regimen	Duration	No. of Patients
TAC	Docetaxel -75 mg/m2 Doxorubicin- 50 mg/m2 Cyclophosphamide -500 mg/m2	6 cycles Day 1 every 3 weeks	62
FAC	Fluorouracil- 500 mg/m2 Doxorubicin- 50 mg/m2 Cyclophosphamide -500 mg/m2	6 cycles Day 1 every 3 weeks	64

Additional treatment

- Radiotherapy which was mandatory after conservative surgery and recommended for patients with tumours >5 cm
- Tamoxifen was given for 5 years to all patients with hormone receptor-positive tumours
- Primary prophylactic G-CSF mandatory in TAC arm

- All patients underwent a Modified Radical Mastectomy (MRM)

Observations and Results

The results obtained were analyzed and interpreted. They were represented in tabulated format. The features represented were clinical patient characteristics, their demography and the tumour characteristics. The side effects were recorded and treated as per standard guidelines. Disease free survival of the patients were also recorded at different time intervals.

Table 2: Patient Characteristics in TAC and FAC arm

Patient Characteristics	TAC	FAC
Randomized patients, n	62	64
Median age, years (range)	40-49	40-49
Age <35 y, n (%)	17.5	16.8
Tumour size, % • ≤2 cm • >2 cm	 ▪ 04.83 ▪ 45.72	 ▪ 04.68 ▪ 44.77
Tumour Grade (%) • 1 • 2 • 3	 ▪ 45.16 ▪ 48.38 ▪ 06.46	 ▪ 46.87 ▪ 46.88 ▪ 06.25
Menopausal Status • Pre-menopausal • Postmenopausal	 ▪ 54.84 ▪ 45.16	 ▪ 54.68 ▪ 45.31

Table 3: Hematologic and non-hematologic toxicities in the two studies

Hematologic and nonhematologic toxicities after completion	TAC	FAC
Hematologic toxicity, % • Grade 2–4 anaemia • Neutropenia • Febrile neutropenia (NCI-CTC) • Thrombocytopenia	 ▪ 24.19 ▪ 33.87 ▪ 03.22 ▪ 29.03	 ▪ 09.37 ▪ 23.43 ▪ 01.56 ▪ 14.06
Non-hematologic toxicity, % • Alopecia • Weight loss • Cardiac complications • Nausea and Vomiting • Diarrhoea • Stomatitis • Peripheral Neuropathy	 ▪ 100.0 ▪ 12.00 ▪ 01.60 ▪ 46.70 ▪ 19.35 ▪ 08.06 ▪ 04.80	 ▪ 100.0 ▪ 07.80 ▪ 01.56 ▪ 53.12 ▪ 21.85 ▪ 09.37 ▪ 00.00

Table 4 TAC Arm at 1 Year

Initial Stage	DFS (%)	Local Recurrence	Systemic Recurrence
IIIA(n=28)	27 (96.42%)	01 (03.57%)	-
IIIB(n=34)	30 (88.23%)	04(11.76%)	-

Table 5 FAC Arm at 1 Year

Initial Stage	DFS (%)	Local Recurrence	Systemic Recurrence
IIIA(n=30)	29 (96.67%)	01 (03.33%)	-
IIIB(n=34)	30 (88.23%)	04 (11.76%)	-

Table 6: TAC Arm at 5 Years

Initial Stage	DFS (%)	Local Recurrence	Systemic Recurrence
IIIA(n=28)	18 (64.28%)	02 (07.14%)	01 (03.57%)
IIIB(n=34)	18 (52.94%)	03 (08.82%)	01 (02.94%)

Table 7: FAC Arm at 5 Years

Initial Stage	DFS (%)	Local Recurrence	Systemic Recurrence
IIIA(n=30)	17 (56.60%)	03 (10.00%)	01 (03.33%)
IIIB(n=34)	15 (44.11%)	02 (05.88%)	01 (02.94%)

Out of the total 126 patients selected, after randomization, 62 patients were selected for TAC arm and 64 patients were selected for FAC arm. The median age range in the both arms was 40-49 years. Percentage of patient's age group less than

35 years was 17.5% in TAC arm as compared to 16.8% in FAC arm. Majority of patients had tumour size more than 2 cm in both groups (45.72% and 44.77% in TAC and FAC arm respectively). Majority of patients in both groups had grade 2 tumor histopathologically (48.38% and 46.88% in TAC and FAC arm respectively), followed by grade 1 tumour (45.16% and 46.87% in TAC and FAC arm respectively).

Majority of patients in both groups were premenopausal (54.84% and 54.68% in TAC and FAC arm respectively). (Table 2)

Most common hematologic toxicity in both groups was neutropenia (33.87% and 23.43% in TAC and FAC arm respectively) followed by thrombocytopenia, anemia and febrile neutropenia. All patients in both groups suffered from alopecia. Other non-hematologic toxicity in decreasing order were nausea/vomiting (46.7% and 53.12% in TAC and FAC arm respectively) followed by diarrhea. Peripheral neuropathy occurred in TAC arm. (Table 3)

After neoadjuvant chemotherapy, surgery, adjuvant chemotherapy and radiation, comparison of results were done for both TAC and FAC arm at 1 year follow up of the completion of the treatment scheme. After 1 year follow up Disease Free Survival (DFS) in TAC and FAC arm were similar in all stages of LABC. No case of systemic recurrence was present in both the study groups. (Table 4 and 5)

After the completion of 5 years of follow up, TAC arm had better Disease-Free Survival (DFS) than FAC arm (64.28% vs 56.60% in stage IIIA in TAC and FAC arm respectively and 52.94% vs 44.11% in stage IIIB LABC in TAC and FAC arm respectively). Local recurrence was higher in FAC arm in stage IIIA patients but lower for stage IIIB LABC patients. Systemic recurrence was similar in both arms. (Table 6 and 7)

Discussion

Breast cancer is the most common cancer and a major cause of cancer mortality in women worldwide[1]. Locally advanced breast carcinomas (LABC) (T3, T4 or N2-N3) have a poor prognosis. Neoadjuvant systemic treatments offer earlier control and eradication of the potential subclinical metastatic foci, shrinkage of the primary tumour (associated with increased rates of resectability and breast conserving surgery), and direct assessment of tumour response to therapy[8]. There is a growing interest in the use of neoadjuvant chemotherapy in premenopausal breast cancer with large (>5 cm) breast tumours to increase the rate of breast conserving surgery[9]. Therefore, neoadjuvant chemotherapy has been considered as the standard of care in premenopausal patients with locally advanced breast cancer, particularly in unresectable disease[8]. Anthracycline-based chemotherapy has been regarded as one of the most efficacious chemotherapy regimens for neoadjuvant treatment in patients with breast cancer. Complete pathologic response to neoadjuvant treatment is a good prognostic factor in women with breast cancer. Doxorubicin is the most active agent used for metastatic breast cancer in clinical practice. Docetaxel also plays an important role. Docetaxel is a highly active agent in breast cancer and has no cross-resistance with doxorubicin[10-12]. Some studies have evaluated the effect of adding taxanes to doxorubicin-based chemotherapy[13,14].

For adjuvant therapy, evidence supports the addition of four cycles of a taxane to four cycles of doxorubicin/cyclophosphamide to improve disease-free and overall survival rates in both node-positive and node negative breast cancer patients [13-16]. In addition, some reports have concluded that TAC improves disease free and overall survival compared to FAC[12,17]. Similar results were observed in our study.

For neoadjuvant therapy, some evidence suggests the superiority of TAC to FAC, and that the combination of docetaxel and cyclophosphamide is an acceptable alternative to treatment with doxorubicin and cyclophosphamide[18-20].

Complete pathologic response, which means no evidence of residual invasive disease in the primary site, correlates with improved survival[9].

In our study, complete clinical and pathologic response rates were significantly higher in the TAC arm.

Post chemotherapy, hematologic complications can be life-threatening[21]. Prophylactic G-CSF is administered to the patients with TAC regimen. Our patients who received TAC were supported by prophylactic G-CSF (filgrastim). 3.22% and 1.56% developed febrile neutropenia in TAC arm and FAC arm respectively.

Two of the most prevalent side effects of chemotherapy are nausea and vomiting. In our study the incidence of nausea and vomiting in the TAC arm was less than in the FAC arm.

Batra et al. compared TAC to FAC and found that oral mucositis, neutropenic fever, diarrhoea and infection was more frequent in the TAC arm.

The frequency of anaemia, thrombocytopenia, nausea, vomiting and abdominal pain was equal in both arms. The difference of results between our study and the trial reported by Batra et al. could be due to G-CSF administration in our study[22].

The limited data of the present study and data from large published trials support a combined doxorubicin and docetaxel regimen for neoadjuvant treatment [1,20, 23].

Conclusion

TAC regimen used for neoadjuvant chemotherapy for locally advanced breast cancers has a better disease-free survival with lesser systemic toxicity as compared to FAC regimen.

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