

# Which is More Effective; Docetaxel, Doxorubicin and Cyclophosphamide or 5-Fluorouracil, Doxorubicin and Cyclophosphamide in Adjuvant Treatment of Early Stage Node Positive Breast Cancer?

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**Abstract:** Background: The aim of this study is to compare the efficacy and the safety of docetaxel, doxorubicin and cyclophosphamide (TAC) with 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) as adjuvant treatment for early stage node positive breast cancer patients. Methods: Sixty patients with pathologically confirmed early stage node-positive breast cancer were randomly assigned to receive six cycles of either docetaxel (75mg/m<sup>2</sup>), doxorubicin (50mg/m<sup>2</sup>) and cyclophosphamide (500mg/m<sup>2</sup>) every three weeks or 5-fluorouracil (500mg/m<sup>2</sup>), doxorubicin (50mg/m<sup>2</sup>) and cyclophosphamide (500mg/m<sup>2</sup>) every three weeks as adjuvant treatment. The two chemotherapy regimens were compared in term of disease free survival (DFS) and overall survival (OS). Results: At a median follow-up of 30 month, the median estimated rate of DFS for patients in the TAC group was 24 month compared to 20 month for patients in the FAC group which was statistically significant (95% confidence interval [CI], 0.49 to 7.17; P <0.04). In terms of OS, no significant difference between the two treatment groups, the median estimated rate of OS in the TAC arm was 25 month compared to 24 month in the FAC arm (CI, 2.84 to 5.27; P= 0.522). No significant difference in DFS as regarding the prognostic factors as number of involved axillary lymph nodes (p=0.485), menopausal status (P=0.684), hormone-receptor status (P=0.795) and HER2/neustatus (P=0.509). The incidence of grade 2-3 anemia was higher in the TAC group than in the FAC group (23.3% versus 13.3%, P<0.04). As regarding neutropenia, it occurred more frequently in the TAC group (13.3% versus 6.7%, P<0.04). The incidence of grade 3 febrile neutropenia in the TAC group was 10% versus 3.3% in the FAC group (P=0.372). Conclusion: Incorporation of docetaxel in the adjuvant treatment of early node-positive breast cancer patients improves the DFS with tolerable toxicity compared to FAC regimen. However, further follow-up is needed to demonstrate its effect on the OS.

**Keywords:** TAC/FAC, adjuvant, node-positive, breast cancer, survival

## 1. Introduction

The most frequently diagnosed cancer and the leading cause of death in women is breast cancer [1]. In the United States breast cancer is the most common malignancy in women and is second to lung cancer as a cause of cancer death. The American Cancer Society estimates that 255,180 Americans will be diagnosed with breast cancer and 41,070 will die of the disease in the United States in 2017 [2]. At presentation the majority of patients are diagnosed at early stages, about 61%, with a 5-year survival about 90%, regionally advanced in 32 %, and metastatic in 7 % of cases [3]. Adjuvant systemic therapy should be considered after surgical treatment based on individual risk of relapse and predicted sensitivity to a particular treatment. The results of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview analysis show convincing reductions in the recurrence and death for adjuvant chemotherapy in all age group [4].

In the mid-1990s the introduction of taxanes in the treatment of metastatic breast cancer (MBC) marked a significant advance [5, 6]. In 1960s paclitaxel was isolated from extracts from pacific yew trees (*Taxus brevifolia*). Docetaxel was discovered in 1980s, a more potent semisynthetic derivative of paclitaxel, derived from extracts of the yew trees (*Taxus baccata*) [7-9].

In 1996 docetaxel received FDA approval for locally advanced and MBC after failure of prior chemotherapy marking a second milestone in the treatment of MBC [10, 11].

Docetaxel has been investigated for early breast cancer as an adjuvant treatment in combination with anthracyclin-containing regimens. After a median follow-up of 124 month of patients with operable node-positive breast cancer, the multicentre phase III randomized Breast Cancer International Research Group (BCIRG) 001 trial showed that six cycles of docetaxel, doxorubicin and cyclophosphamide (TAC) was significantly more effective than six cycles of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) for the adjuvant treatment reducing the risk of recurrence by 28% and the risk of death by 30%. The benefit in DFS was irrespective of nodal, hormone receptor, and HER2 status but TAC was associated with considerably more toxicity, including febrile neutropenia [12,13]. The present study compares the efficacy of TAC with FAC as adjuvant chemotherapy in women with early, axillary lymph node-positive, breast cancer.

## 2. Patients and Methods

### Study Population

This prospective phase III clinical randomized study was conducted at the Clinical Oncology Department in Assiut

University Hospital from 2014 to 2017. The Ethics Committee of Faculty of Medicine, Assiut University approved this protocol before data collection. Sixty female patients with pathologically confirmed early breast cancer (clinical stage I, II, IIIA according to AJCC) [14], were included in the study. Patients eligible for the study were between 18 and 70 years of age, in good general condition, had undergone primary surgery (lumpectomy with free surgical margins or mastectomy plus axillary-node dissection including at least 10 lymph nodes), all patients had at least one axillary lymph node positive for cancer on histological examination. Complete staging workup was done including chest radiography, abdominal ultrasonography, computed tomography, or both, and bone scan when indicated. Assessment of the left ventricular ejection fraction with echocardiography was mandatory.

#### Study design

Patients were classified into two groups; the first group received intravenous infusion of TAC (docetaxel 75mg/m<sup>2</sup>, Adriamycin 50mg/m<sup>2</sup> and cyclophosphamide 500mg/m<sup>2</sup>). The second group received intravenous infusion of FAC (5-Fluorouracil 500mg/m<sup>2</sup>, Adriamycin 50mg/m<sup>2</sup> and cyclophosphamide 500mg/m<sup>2</sup>) every three weeks for six cycles. Patients on TAC received premedication dexamethasone 8mg p.o. every 12 hours for six doses starting the day before chemotherapy to prevent docetaxel-related hypersensitivity and fluid retention. Antiemetic drug was recommended for both groups.

The primary end point was DFS, defined as the time from randomization to the date of clinical relapse. Second end point was OS, defined as the time from randomization until death.

#### Evaluation

Toxicity was assessed before each cycle and evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (NCI-CTCAE).

On day 21 of each cycle, complete blood cell count and clinical assessments, including those for toxic effects were performed. Follow-up visits took place every 3 months during the period of the study.

Chest radiography and abdominal ultrasonography were performed every 6 months mammography was repeated annually during the follow-up period.

#### Statistics

The statistical analysis was done with the Statistical Package for the Social Sciences, version 16 (SPSS, Inc., Chicago, IL, USA). The descriptive analysis was done. The Kaplan-Meier survival curves were used for estimation of DFS and OS. P values less than 0.05 was considered significant.

### 3. Results

A total of sixty patients were randomly enrolled in our study and all of them completed six cycles of chemotherapy successfully. The baseline demographic data of our patients

were summarized in Table 1. The mean age in the TAC group was 46.4±9.8 years, and 45.7±10.3 years in the FAC group. No significant difference was noticed between the study groups in terms of age, tumor characters, menopausal status and the type of surgery. Table 2 shows the toxicity of the treatment in both groups, the most common toxicity was nausea and vomiting. Almost all patients had alopecia. The incidence of grade 2-3 anemia was higher in the TAC group than in the FAC group (23.3% versus 13.3%, P<0.04). As regarding to the neutropenia, it occurred more in the TAC group (13.3% versus 6.7%, P<0.04). The incidence of grade 3 febrile neutropenia in the TAC group was 10% versus 3.3% in the FAC group (P=0.372).

After 30 month of follow up of patients, the median estimated rate of DFS for patients in the TAC group was 24 month compared to 20 month for patients in the FAC group which was statistically significant (CI, 0.49 to 7.17; P<0.04) Table 3 and figure 1. In terms of OS, no significant difference between the two treatment groups, the median estimated rate of OS in the TAC arm was 25 month compared to 24 month in the FAC arm (CI, 2.84 to 5.27; P=0.522) Table 4 and figure 2. Table 5 shows the analysis of the impact of the prognostic factors on the DFS and OS revealed that there was no significant difference as regarding the number of involved axillary lymph nodes (p=0.485), menopausal status (P=0.684), hormone-receptor status (P=0.795) and HER2/neu status (P=0.509).

**Table 1:** Patients and disease characteristics of the studied groups

| Character                        | TAC<br>(N=30) | FAC<br>(N=30) | P<br>value |
|----------------------------------|---------------|---------------|------------|
| <b>Age</b>                       |               |               |            |
| Mean age (year)                  | 46.4±9.8      | 45.7±10.3     | P=0.378    |
| <b>Tumor size-no. (%)</b>        |               |               |            |
| ≤2cm                             | 6(20.0)       | 4(13.33)      | P=0.592    |
| >2 to 5cm                        | 19(63.33)     | 22(73.33)     |            |
| >5cm                             | 5(16.67)      | 4(13.33)      |            |
| <b>Tumor grade-no. (%)</b>       |               |               |            |
| Grade 1                          | 1             | 2             | P=0.408    |
| Grade 2                          | 6             | 4             |            |
| Grade 3                          | 23            | 24            |            |
| <b>N stage</b>                   |               |               |            |
| N1(1-3)                          | 10(33.33)     | 9(30.0)       | P=0.372    |
| N2(4-10)                         | 18(60.0)      | 20(66.67)     |            |
| N3(>10)                          | 2(6.67)       | 1(3.33)       |            |
| <b>Histology</b>                 |               |               |            |
| IDC                              | 29(96.67)     | 30(100.0)     | P=0.446    |
| ILC                              | 1(3.33)       | 0(0)          |            |
| <b>Menopausal status-no. (%)</b> |               |               |            |
| Premenopausal                    | 18(60.0)      | 16(53.33)     | P=0.273    |
| Postmenopausal                   | 12(40.0)      | 14(46.67)     |            |
| <b>ER/PR status-no. (%)</b>      |               |               |            |
| ER+/PR+                          | 19(63.33)     | 17(56.67)     | P=0.583    |
| ER+/PR-                          | 5(16.67)      | 8(26.67)      |            |
| ER-/PR+                          | 3(10)         | 3(10.0)       |            |
| ER-/PR-                          | 3(10)         | 2(6.67)       |            |
| <b>Her 2-neu-no. (%)</b>         |               |               |            |
| Positive                         | 19(63.33)     | 18(60.0)      | P=0.336    |
| Negative                         | 11(36.67)     | 12(40.0)      |            |
| <b>Surgery-no. (%)</b>           |               |               |            |
| Breast-conserving surgery        | 5(16.67)      | 6(20.0)       | P=0.362    |
| Mastectomy                       | 25(83.33)     | 24(80.0)      |            |

**Table 2: Treatment Toxicity**

| <i>Toxic Effect</i>   | <i>TAC(N=30)<br/>no.(%)</i> | <i>FAC (N=30)<br/>no.(%)</i> | <i>P- value</i> |
|-----------------------|-----------------------------|------------------------------|-----------------|
| <i>Hematologic</i>    |                             |                              |                 |
| Anemia                | 7(23.33)                    | 4(13.33)                     | P<0.04*         |
| Leukopenia            | 5(16.67)                    | 3(10.0)                      | P=0.0224        |
| Thrombocytopenia      | 2(6.67)                     | 0(0)                         | P=0.371         |
| Neutropenia           | 4(13.33)                    | 2(6.67)                      | P<0.04*         |
| Febrile neutropenia   | 3(10.0)                     | 1(3.33)                      | P=0.372         |
| Neutropenic infection | 1(3.33)                     | 0(0)                         | P=0.694         |
| <i>Nonhematologic</i> |                             |                              |                 |
| Nausea and vomiting   | 27(90.0)                    | 28(93.33)                    | P=0.254         |
| Diarrhea              | 5(16.67)                    | 3(10.0)                      | P=0.335         |
| Alopecia              | 30(100.0)                   | 30(100.0)                    | P=1             |
| stomatitis            | 3(10.0)                     | 5(16.67)                     | P=0.0224        |
| Irregular menses      | 18(60.0)                    | 16(53.33)                    | P=0.846         |
| Amenorrhea            | 13(43.33)                   | 12(40.0)                     | P=0.684         |
| Nail disorder         | 3(10.0)                     | 1(3.33)                      | P=0.372         |

**Table 3: Means and Medians for Survival Time**

| group   | Mean <sup>a</sup> |            |                         |             | Median   |            |                         |             |
|---------|-------------------|------------|-------------------------|-------------|----------|------------|-------------------------|-------------|
|         | Estimate          | Std. Error | 95% Confidence Interval |             | Estimate | Std. Error | 95% Confidence Interval |             |
|         |                   |            | Lower Bound             | Upper Bound |          |            | Lower Bound             | Upper Bound |
| 1       | 22.100            | 1.411      | 19.334                  | 24.866      | 24.000   | 1.095      | 21.853                  | 26.147      |
| 2       | 18.759            | 1.290      | 16.230                  | 21.287      | 20.000   | 2.355      | 15.385                  | 24.615      |
| Overall | 20.458            | .974       | 18.548                  | 22.367      | 23.000   | .843       | 0.49                    | 7.17        |

a. Estimation is limited to the largest survival time if it is censored.

**Table 4: Means and Medians for Survival Time**

| Group   | Mean <sup>a</sup> |            |                         |             | Median   |            |                         |             |
|---------|-------------------|------------|-------------------------|-------------|----------|------------|-------------------------|-------------|
|         | Estimate          | Std. Error | 95% Confidence Interval |             | Estimate | Std. Error | 95% Confidence Interval |             |
|         |                   |            | Lower Bound             | Upper Bound |          |            | Lower Bound             | Upper Bound |
| 1       | 22.800            | 1.403      | 20.050                  | 25.550      | 25.000   | 1.369      | 22.316                  | 27.684      |
| 2       | 21.586            | 1.465      | 18.715                  | 24.458      | 24.000   | .663       | 22.700                  | 25.300      |
| Overall | 22.203            | 1.008      | 20.228                  | 24.179      | 24.000   | .768       | 2.84                    | 5.27        |

a. Estimation is limited to the largest survival time if it is censored.

**Table 5: Disease-free Survival analysis according to the prognostic factors**

|                          | No. of all Patients (%) | TAC (N=30) no. (%) | FAC (N=30) no. (%) | P-value |
|--------------------------|-------------------------|--------------------|--------------------|---------|
| <b>N stage</b>           |                         |                    |                    |         |
| N1                       | 19(31.67%)              | 10(33.33%)         | 9(30.0%)           | P=0.485 |
| > N1                     | 41(68.33%)              | 20(66.67%)         | 21(70.0%)          |         |
| <b>Menopausal status</b> |                         |                    |                    |         |
| Premenopausal            | 34(56.67%)              | 18(60.0%)          | 16(53.33%)         | P=0.684 |
| Postmenopausal           | 26(43.33%)              | 12(40.0%)          | 14(46.67%)         |         |
| <b>ER/PR status</b>      |                         |                    |                    |         |
| Positive                 | 55(91.67%)              | 27(90.0%)          | 28(93.33%)         | P=0.795 |
| Negative                 | 5(8.33%)                | 3(10.0%)           | 2(6.67%)           |         |
| <b>HER2/neu status</b>   |                         |                    |                    |         |
| Positive                 | 37(61.67%)              | 19(63.33%)         | 18(60.0%)          | P=0.509 |
| Negative                 | 23(38.33%)              | 11(36.67%)         | 12(40.0%)          |         |

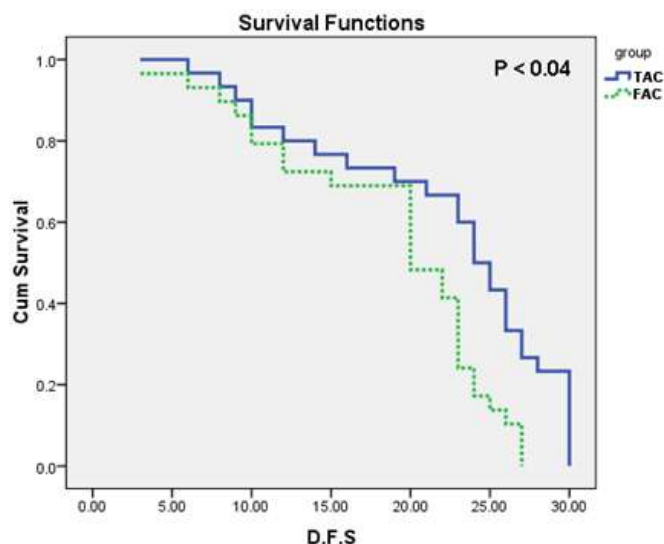


Figure 1: Kaplan-Meier curve for disease free survival

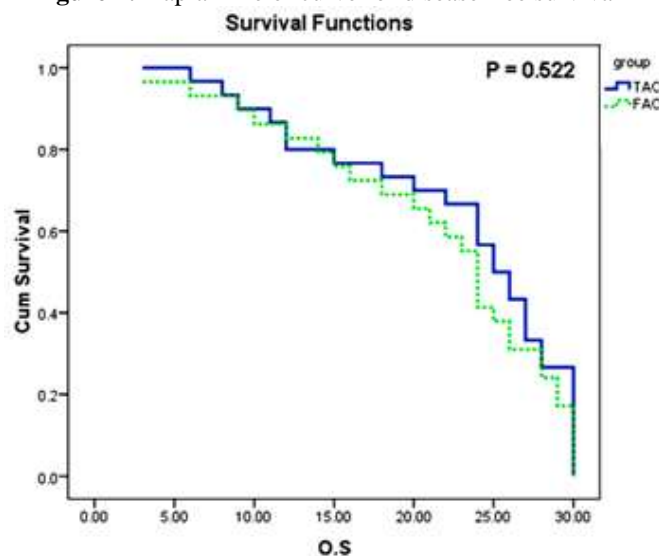


Figure 2: Kaplan-Meier curve for over-all survival

#### 4. Discussion

A recent therapeutic advance for the adjuvant treatment of breast cancer was the use of taxanes [paclitaxel (P) or docetaxel (T)]. Several randomized clinical trials (RCTs) evaluate the taxanes with anthracycline-based regimens. In the present evidence review, trials of taxanes represented the largest number of RCTs (fifty-five trials in ninety-three publications) but the EBCTCG was the most completed one [4]. The hazard ratios (HRs) for DFS and OS of many of these trials showed that taxane-based therapy was associated with significant reduction in the risk of recurrence and death. This meta-analysis indicated that taxane-based adjuvant chemotherapy was more efficacious in improving DFS and OS when compared with taxane-free therapy [11,15-21].

In 2004, docetaxel was approved in combination with doxorubicin and cyclophosphamide for patients with node-positive operable breast cancer [22, 23].

Our clinical randomized phase III trial comparing the TAC with the FAC as adjuvant treatment for patients with node-positive early breast cancer showed that, there was improvement in the median DFS for patients in the TAC

group compared to the median DFS for patients in the FAC group (CI, 0.49 to 7.17;  $P < 0.04$ ).

These results are similar to the final results from BCIRG 001 trial which showed TAC is superior to FAC, estimated 5-year DFS was 75% with TAC and 68% with FAC (HR, 0.72; 95% CL, 0.59-0.88;  $P = 0.01$ ); survival was 87% with TAC and 81% with FAC (HR, 0.70; 95% CL, 0.53-0.91;  $P = 0.008$ ) [11]. However in terms of OS, the present study showed that there was no significant difference between the two groups ( $P = 0.522$ ) which differ from the results of the previous trials this may be due to the short duration of follow-up of our study [11]. The 10-year updated results of the Eastern Cooperative Oncology Group (ECOG) 1199 trial which compared patients with node-positive or high risk node-negative breast cancer who received 4 cycles of Adriamycin and cyclophosphamide (AC) followed by either paclitaxel or docetaxel, either weekly or every 3 weeks showed that, incorporation of weekly paclitaxel and docetaxel every 3 weeks was associated with significant improvement in DFS and marginal improvement in OS, compared with paclitaxel every 3 weeks [24].

Jones et al 2009 reported that at a median follow-up of 7 years of women with stage I to III breast cancer, the DFS and OS were improved with docetaxel and cyclophosphamide (TC) compared with Adriamycin and cyclophosphamide (AC) [25].

After a median follow-up of 84 month of 1,016 patients with operable breast cancer who were assigned to four 3-week cycles of AC or docetaxel and cyclophosphamide (DC), the US Oncology Research phase III trial found that there was significant improvement in the DFS (HR, 0.74;  $P = 0.033$ ) and OS (HR, 0.69;  $P = 0.032$ ) [25].

The results of analysis of the impact of the prognostic factors as number of axillary lymph node, menopausal status, ER/PR status and HER2/neu on the DFS indicated that there was no significant improvement in DFS in the TAC arm compared to the FAC arm this maybe due to the small number of patients and the short duration of follow-up. These results are consistent with the results of the BCIRG001 that did not find any correlation between the benefit in DFS and the nodal, hormone receptor, and HER2/neu status and adjuvant docetaxel [11, 13, 26]. Martin et al 2005 and Roche et al 2006 demonstrated that the benefits of taxanes may be lower, if not negligible, for N4+ [11, 27] and for ER- positive patients [28-32].

Hayes et al reported that increase in the taxanes response in ER negative patients [33]. Other previous studies demonstrated that taxanes and anthracycline are more effective in triple negative breast cancer (TNBC) [33-35].

Drug-related toxicities, such as anemia, neutropenia, febrile neutropenia and other non- hematological toxicities were reported in this study and in other previous studies [36]. TAC was associated with marked toxicities as anemia and neutropenia ( $P < 0.04$ ) and were manageable with standard supportive measures.



## 5. Conclusion

In patients with node-positive early breast cancer TAC provides improvement in DFS with manageable toxicity compared with FAC. However, further follow-up is needed to demonstrate its effect on the OS.

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