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ORIGINAL ARTICLE

A retrospective analysis of adjuvant CAF, AC-T and TAC regimens in triple negative early stage breast cancer

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Summary

Purpose: *To compare the effectiveness of adjuvant chemotherapy regimens in triple negative breast cancer (TNBC) for which no protocol has been determined to be treatment of choice.*

Methods: *In this single-center retrospective trial, we analyzed the adjuvant regimens of 164 TNBC patients among 3253 breast cancer patient records. Adjuvant TAC (docetaxel, doxorubicin, cyclophosphamide), CAF (cyclophosphamide, doxorubicin, 5fluorouracil), and AC-T (doxorubicin, cyclophosphamide followed by docetaxel) regimens were compared in terms of disease free survival (DFS) and overall survival (OS).*

Results: *In terms of both DFS and OS TAC was significantly superior to AC-T in node positive TNBC. When node negative and positive patients were analyzed together, TAC was still significantly superior to AC-T in terms of DFS and OS. There was a trend favoring CAF over AC-T, however, it was only significant in terms of OS when all node negative and positive TNBC patients were incorporated together.*

Conclusion: *In the adjuvant setting, especially in node positive patients, TAC should be the treatment of choice in TNBC patients. CAF is probably better than AC-T in TNBC.*

Key words: *adjuvant chemotherapy, survival, TAC/CAF/AC-T, triple negative breast cancer*

Introduction

Breast cancer is a global health issue and is the most common type of cancer in females around the world. One in 8 women develops breast cancer in her lifetime. In the last two decades breast cancer incidence has remained steady. In contrast, mortality rates have been decreasing constantly in these decades [1]. The main reason for the decreased mortality is probably due to improvements in the adjuvant treatments and screening techniques [2].

Adjuvant therapy reduces the recurrence and mortality rates in breast cancer [1,3]. On the other hand, not all patients benefit equally from adjuvant chemotherapy. Estrogen receptor negative patients benefit more from chemotherapy than ER positive patients do [4]. There is no single standard adjuvant chemotherapy regimen in breast cancer; chemotherapy choices are influenced mainly by hormonal and HER2 status, age, comorbidities, tumor grade and nodal involvement.

TNBC accounts for approximately 10-20% of breast cancers [5]. TNBC tends to be more aggressive than other histological types, it is usually high-grade and the most common histology is invasive ductal carcinoma. Moreover, TNBC is associated with high recurrence rates, and its metastases tend to grow and spread more rapidly than the other histological types of breast cancer [3,6]. Therefore, determining the most effective adjuvant treatment is of great importance in

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Table 1. Patient and disease characteristics of the treatment groups

Characteristics	*TAC N (%)*	*CAF N (%)*	*AC-T N (%)*	*p value*
Age, years (±SD)	44.5 ± 9.3	46.7 ± 9.3	43.4 ± 10.5	ns
T stage				
T1	13 (21)	16 (28.1)	10 (25.6)	ns[1]
T2	38 (61.3)	34 (59.6)	20 (51.3)	ns[1]
T3	11 (17.7)	7 (12.3)	8 (20.5)	ns[1]
T4	0	0	1 (2.6)	N/A[2]
N stage				
N0	6 (9.4)	39 (65)	6 (15)	N/A[3]
N1	33 (51.6)	14 (23.3)	13 (32.5)	ns[4]
N2	10 (15.6)	4 (6.7)	8 (20)	ns[4]
N3	14 (21.9)	2 (3.3)	11 (27.5)	ns[4]
ND[4]	1 (1.6)	2 (5.9)	1 (1.7)	ns[4]
Pre-/Postmenaupause	41/23 (64/36)	40/20 (67/33)	28/12 (70/30)	ns
Grade 1/2/3	1/14/48 (1.6/22.2/76.2)	3/15/34 (5.8/28.8/65.4)	2/9/26 (5.4/24.3/70.3)	ns
Histology				
IDC	56 (87.5)	50 (83.3)	33 (82.5)	ns
ILC	0	3 (5)	1 (2.5)	ns
Mixed-other	8 (12.4)	7 (11.7)	6 (15)	ns

ns: not significant, N/A: not applicable, [1]T1, T2 and T3 groups analyzed as a whole, [2,3]Between-group analyses for T4 and N0 were not possible, [4]N1-2-3 and ND groups analyzed as a whole. IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma

TNBC.

Systemic chemotherapy is the mainstay of the adjuvant treatment in TNBC. However, currently there is no standard chemotherapy regimen that is specifically used in TNBC. Anthracycline and taxane based regimens are commonly used, given their significant efficacy in TNBC [3]. In this retrospective study we analyzed the adjuvant chemotherapy regimens that were applied in our institute.

Methods

Patients and inclusion/exclusion criteria

According to the patient records of Hacettepe University School of Medicine, Oncology Institute, among 3232 breast cancer patients treated/followed between 2003 and 2014 164 (5%) with TNBC and were analyzed with respect to the adjuvant treatments given. TNBC patients who received CAF, AC-T and TAC regimens were included into the analyses. Patients who had serious comorbidities (including chronic kidney disease, functional congestive heart failure, recent myocardial infarction, uncontrolled diabetes mellitus and hypertension), and patients who had diseases that could interfere with chemotherapy administration were excluded. In addition, patients with unknown or suspected ER, PR and HER2 status were excluded. The same staff followed all patients periodically within the recommended follow-up time periods.

The study end-points were DFS and OS.

Treatment doses and schedules

AC-T was given as the classical schedule, with doxorubicin 60 mg/m^2 and cyclophosphamide 600mg/m^2 every 21 days for 4 cycles, and docetaxel 100 mg/m^2 every 21 days for a further 4 cycles [7)]. CAF was given as cyclophosphamide 600 mg/m^2, doxorubicin 60 mg/m^2, and 5-fluorouracil 600 mg/m^2 every 28 days for 6 cycles [8]. TAC was given as docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 21 days for 6 cycles [9]. Hematopoietic growth factors were given as necessary.

Staging and Immunohistochemistry

Pathological and clinical staging at diagnosis was defined according to the American Joint Committee on Cancer (7th Edn) [10]. Tumor grade was defined based on the Bloom-Richardson criteria as I, II, III, and other/unknown [11]. ER and PR status was recorded on the basis of immunohistochemistry (IHC) (positive when 1% of tumor cells stained positive with IHC, and negative). Assessments for the HER2 score were recorded based on the IHC score (negative: 0 and 1+, positive:

Table 2. Results of the bivariate Cox regression model in node positive and negative (N=0-3) TNBC patients

	Hazard ratio	*Standard error*	*Wald chi-square*	*95 % confidence interval*	*p value*
DFS					
TAC vs AC-T	0.30	0.41	8.07	1.37 - 0.69	0.004
TAC vs CAF	0.60	0.42	1.41	0.26 - 1.38	0.22
CAF vs AC-T	0.57	0.33	2.85	0.29 - 1.09	0.091
OS					
TAC vs AC-T	0.38	0.48	4.06	0.14 - 0.97	0.044
TAC vs CAF	0.96	0.51	0.005	0.35 - 2.65	0.94
CAF vs AC-T	0.39	0.39	5.63	0.18 - 0.85	0.018

DFS: disease free survival, OS: overall survival, TNBC: triple negative breat cancer

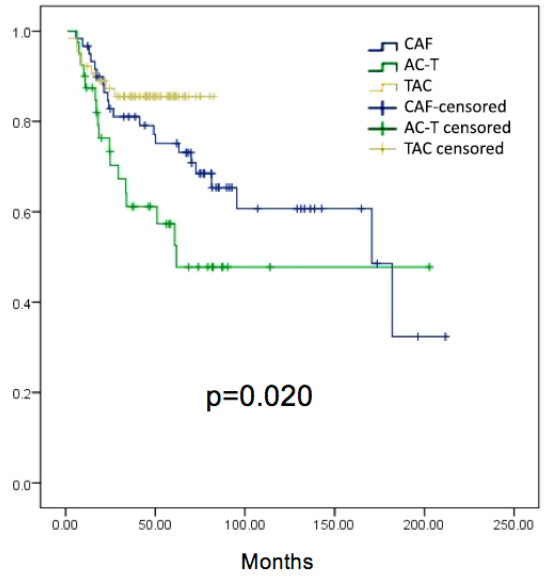

Figure 1. Disease free survival plot (all N stages included).

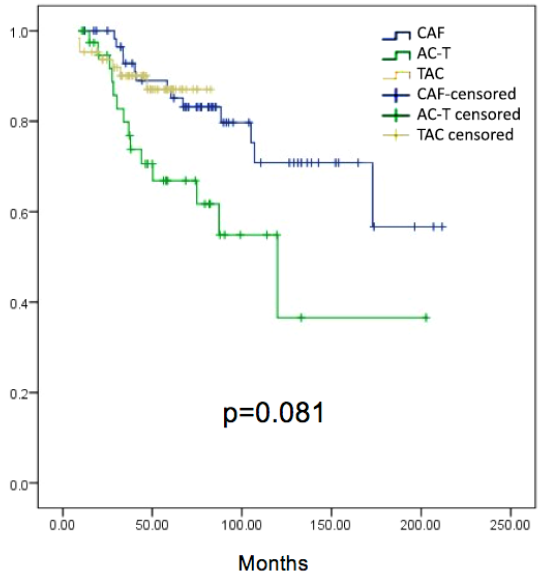

Figure 2. Overall survival plot (all N stages included).

3+) and the ratio of HER2 to chromosome 17 signaling according to the American Society of Clinical Oncology-College of American Pathologists (ASCOCEP) guidelines. Specimens scored 2+ were further evaluated by fluorescence in situ hybridization (FISH) technique. HER2 amplification was defined as a ratio of HER2 to chromosome 17 signaling that was more than 2.2 [12].

Statistics

All analyses were performed with two-sided p values. Differences between categorical variables were analyzed by Pearson's Chi-square test, and differences between continuous variables were analyzed by using independent t-test or one-way ANOVA test where suitable. Kaplan-Meier analysis was used to construct life-table plots. Statistical differences between groups were analyzed with log-rank test. In comparing the chemotherapy regimens in terms of DFS and OS, we estimated the risk ratio associated with an event and calculated the 95% confidence interval (95% CI) from the Cox proportional-hazards model. Analyses were conducted using the Statistical Package for Social Sciences (SPSS, version 22) software. Differences at $p<0.05$ were considered significant.

Results

Triple negative node positive and negative group (N0-3)

TNBC patients included in the analyses received the following regimens: CAF N=60, AC-T N=40 and TAC N=64. Mean age was 46.7±9.3 years in the CAF group, 43.4±10.5 in the AC-T group, and 44.5±9.3 in the TAC group. No difference was noticed between treatment groups in terms of age. The same applied to menopausal status, tumor grade and histological types. Demographic features are shown in Table 1. In terms of DFS, when all N stages (N0, N1, N2 and N3) were included, TAC was significantly superior to AC-T (p=0.03). but was no better than CAF. In addition, there was a trend favoring CAF when compared to

Table 3. Results of bivariate Cox regression model in node positive (N=1-3) TNBC patients

	Hazard ratio	*Standard error*	*Wald chi-square*	*95 % confidence interval*	*p value*
DFS					
TAC vs AC-T	0.25	0.43	9.76	0.10 - 0.60	0.002
TAC vs CAF	0.47	0.52	1.99	0.17 - 1.33	0.15
CAF vs AC-T	0.61	0.42	1.30	0.26 - 1.41	0.25
OS					
TAC vs AC-T	0.31	0.51	5.16	0.11 - 0.85	0.023
TAC vs CAF	0.91	0.68	0.016	0.24 - 3.47	0.89
CAF vs AC-T	0.53	0.46	1.90	0.21 - 1.30	0.16

For abbreviations see footnote of Table 2

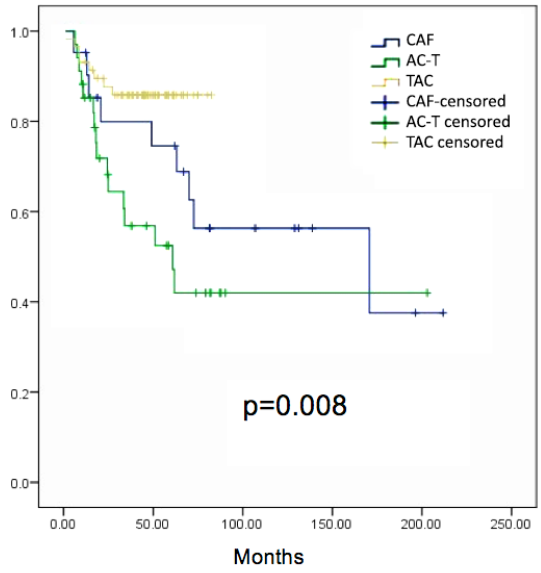

Figure 3. Disease free survival plot (node positive patients included).

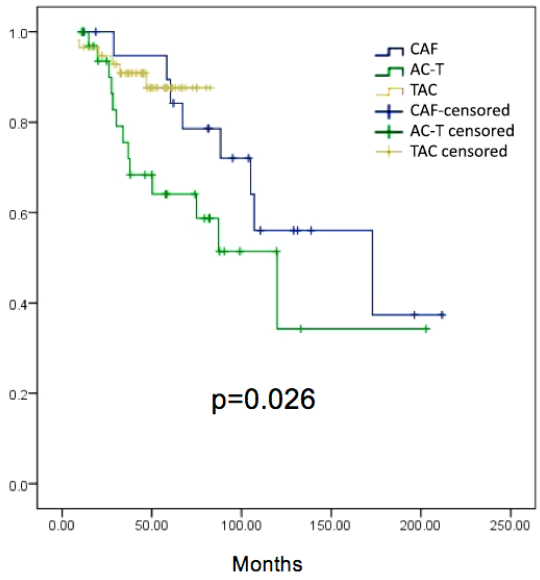

Figure 4. Overall survival plot (node positive patients included).

AC-T, yet without statistical significance (p=0.87) (Figure 1). In terms of OS, when all N stages (N0, N1, N2 and N3) were included, TAC was significantly superior to AC-T and CAF (p=0.037 and p=0.005, respectively). Besides, CAF was significantly better than AC-T (p=0.014) in terms of OS. Bivariate Cox regression analyses demonstrating the hazard ratios of the chemotherapy regimens comparisons are shown in Table 2 and the corresponding DFS and OS plots are shown in Figures 1 and 2.

Triple negative node positive group (N1-3)

When node positive (N1, N2 and N3) TNBC patients were considered; in terms of DFS, TAC was superior to ACT (p=0.001). No significant differences were registered between TAC and CAF, and CAF and AC-T. In terms of OS, TAC was significantly better than ACT (p=0.017). CAF was no better than AC-T, although there was a trend favoring CAF (Table 3, Figures 3 and 4).

Discussion

In those kinds of cancer where systemic adjuvant treatment is considered advantageous, the general concept is to choose the most effective adjuvant treatment with acceptable toxicity in order to decrease the odds for recurrence and metastasis. However, there has been no consensus yet about which chemotherapy regimen is the best option in TNBC. This issue is fairly important since recurrence rates are higher in TNBC than they are in other histological types of breast cancer. Furthermore, once recurrence occurs, TNBC behaves more aggressively. Therefore, this study presents several important results that may influence clinical practice.

While interpreting the results, the most important limitation was that most of the CAF-given patients were node negative, hence the small

sample of node positive CAF-given patients might have caused misleading results. As we mentioned above we did not present node negative results because of the inadequate sample size. In node positive patients the differences between the 3 groups were not significant, however CAF-given patients had the lowest sample size. Therefore, the results of this study might not be instructive in terms of CAF comparisons, however, the comparisons between TAC and AC-T is conclusive since the distributions of TAC and AC-T in N and T stages were adequate to draw conclusions.

One of the most important findings was that TAC regimen showed the best DFS in node positive TNBC patients. Besides, the striking result was that AC-T regimen showed the worst DFS in the same patient group. There has been no randomized study that compares AC-T, TAC and CAF regimens specifically in TNBC population. In the BCIRG 001 trial Martin et al. compared adjuvant TAC and FAC regimens in node positive patients and showed favorable results with TAC in terms of DFS and OS. However, in this study no TNBC subgroup was analyzed separately [9]. In the GEICAM 9805 trial, Martin et al. studied adjuvant docetaxel in high risk node negative breast cancer patients [13]. They compared TAC and FAC regimens in hormone positive and negative subgroups. In ER positive and HER2 negative, ER positive and HER2 positive, and ER negative and HER2 positive groups they found no difference between TAC and FAC regimens. However, in the triple negative group TAC was superior to FAC. In our study the best response was seen in the TAC group, although it did not reach statistically significant level as compared to CAF with regards to DFS. On the other hand, TAC was significantly better than ACT in terms of DFS in all analyses. This was one of the most important results of the present study.

When it comes to OS rates, TAC was significantly superior AC-T. In this study AC-T seems to be the most ineffective regimen. In the BCIRG 001 study, as we mentioned above, there was also a significant OS difference between TAC and CAF regimens which is similar to the results of our study [9]. Hayes et al. showed that response to taxanes increases in ER negative patients [14]. In addition, anthracycline and taxane based treatments are known to be effective in TNBC [3,14,15]. However, the important point in our study is the timing of anthracycline and taxane treatments. TAC and AC-T include the same agents, however TAC is significantly superior to AC-T in terms of DFS and OS. A reasonable explanation in this issue might be the increased effectiveness of intense chemotherapy in high grade and less differentiated tumors. Paired comparisons with CAF may be suggested, yet they should be interpreted according to the aforementioned limitations.

The present study has a few other limitations. First, it is its retrospective nature, although the study groups were almost homogeneous and the patients were regularly followed by the same staff. Second, we could not evaluate the regimens' efficacy in triple negative node negative patients because of the limited sample size in this subgroup. The last limitation is the lack of data in some records about toxicity and safety. However, the adverse effects and toxicity profiles of these chemotherapy regimens are well known; actually we did not observe different range of toxicities.

In conclusion, several considerable points arose from this study. First, this is the first analysis of 3 regimens (TAC, AC-T, and CAF) in TNBC in the adjuvant setting. Second, even though our data are retrospective, TAC is clearly superior to AC-T, and probably better than CAF. Third, it seems that triplet regimens are more effective than doublet sequential treatment. Prospective studies are needed to draw clear conclusions.

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