

Non-anthracycline-containing docetaxel and cyclophosphamide regimen is associated with sustained worse outcome compared with docetaxel, anthracycline and cyclophosphamide in neoadjuvant treatment of triple negative and HER2-positive breast cancer patients: updated follow-up data from NATT study

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Abstract

Objective: A previous study demonstrated that non-anthracycline-containing docetaxel plus cyclophosphamide (TC) regimen was inferior to docetaxel, anthracycline and cyclophosphamide (TAC) in neoadjuvant treatment of triple-negative breast cancer (TNBC) and human epidermal growth factor receptor-2-(HER2)-positive breast cancer in a short-term follow-up. Herein, long-term follow-up survival outcomes have been investigated.

Methods: TNBC or HER2-positive patients were randomized to receive 6 cycles of TC or TAC neoadjuvant treatment. The primary endpoint was pathological complete remission (pCR). Secondary endpoints included clinical response rate, event-free survival (EFS), and overall survival (OS).

Results: A cohort of 96 patients consisted of 45 in TC and 51 in TAC arm. With a median follow-up period of 53 (range, 8–76) months, the patients achieving pCR post neoadjuvant chemotherapy exhibited superior EFS and OS than patients without pCR ($P < 0.05$). TAC treatment resulted in consistently better EFS than TC treatment: the estimated 5-year EFS was 66.1% vs. 29.8% ($P = 0.002$). Moreover, the estimated 5-year OS was also in favor of TAC: 88.4% vs. 51.6% ($P < 0.001$). Multivariable analysis demonstrated that the treatment regimen was an independent prognostic factor, and patients treated with TAC had a superior EFS [hazard ratio (HR), 0.48; 95% confidence interval (95% CI), 0.26–0.90; $P = 0.021$] and OS (HR, 0.20; 95% CI, 0.08–0.60; $P = 0.003$).

Conclusions: The updated long-term follow-up data demonstrated a sustained benefit in EFS and OS from anthracycline-containing TAC treatment, indicating that anthracycline is an essential and effective drug in this clinical trial.

Keywords: Breast cancer; neoadjuvant chemotherapy; anthracycline; survival; triple negative; HER2

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Introduction

Adjuvant systemic chemotherapy has significantly improved the prognosis of breast cancer patients. For patients with

locally advanced breast cancer, neoadjuvant chemotherapy is considered as the standard therapy that can improve surgical options (1). Breast cancer patients who achieved pathological complete remission (pCR) after neoadjuvant

therapy had a superior outcome compared with those without pCR, especially in triple-negative breast cancer (TNBC) or human epidermal growth factor receptor-2 (HER2)-positive breast cancer. This may offer the opportunity to investigate the chemosensitivity of the potential novel treatment in an *in vivo* test (2,3).

Anthracycline- and taxane-based regimens are recommended as the standard neoadjuvant chemotherapy in breast cancer patients (4). In adjuvant chemotherapy setting, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has displayed that adding taxane to anthracyclines can further reduce the disease recurrence and death in comparison with the anthracycline-based regimens (5). However, several studies, including U.S. Oncology (USO) 9735 trial (6), a meta-analysis (7), and the MA.21 trial subgroup analysis (8), demonstrated that anthracycline-containing regimens were not superior to non-anthracycline-containing regimens in HER2-negative breast cancer patients. Moreover, non-anthracycline-containing docetaxel, carboplatin and trastuzumab (TCH) regimen showed similar efficacy compared with the doxorubicin plus cyclophosphamide followed by docetaxel plus trastuzumab (ACTH) regimen in HER2-positive early breast cancer patients (9). In addition, the usage of anthracyclines was associated with the irreversible cardiac toxicity and severe gastrointestinal side effects (10), which challenged the role of anthracyclines in systemic chemotherapy of breast cancer.

Our previously published phase III randomized trial (NATT) showed that the pCR rate was numerically higher in TNBC or HER2-positive breast cancer patients treated with anthracycline-containing docetaxel, anthracycline and cyclophosphamide (TAC) than docetaxel plus cyclophosphamide (TC) regimen (11). With a median follow-up period of 20 months, TAC treatment was associated with a superior event-free survival (EFS) outcome than the TC treatment, especially in TNBC patients, which leads to a premature cessation of recruitment for the trial studies. The joint analysis of Anthracyclines in Breast Cancer (ABC) trials also failed to demonstrate the non-inferiority of non-anthracycline-containing TC regimen compared with taxanes and doxorubicin plus cyclophosphamide (AC) regimens in HER2-negative patients (12).

To further validate our previous follow-up findings, we continued to follow up the patients who had been enrolled in and completed the neoadjuvant treatment. Here, we reported our updated long-term follow-up data about the NATT study to examine the role of anthracycline in

neoadjuvant treatment of TNBC and HER2-positive breast cancer patients.

Materials and methods

Patients

The NATT study was carried out between May 2009 and December 2011, as described previously (11). Briefly, NATT trial was a multicenter, open-label, randomized, non-inferiority, and phase III study in women with TNBC or HER2-positive breast cancer. Estrogen receptor (ER)- or progesterone receptor (PR)-positive was defined as not less than 1% tumor cells with positive cell nuclear staining. HER2-positive breast cancer was defined as HER2 3+ by immunohistochemistry (IHC) or amplification by fluorescence *in situ* hybridization (FISH). TNBC was defined as ER, PR and HER2 negativity. Patients with stage IIB or III disease according to the American Joint Committee on Cancer (AJCC) staging system (version 6) were eligible for participation in the present study. All patients provided written informed consent before randomization. The Ethical Committee/Institutional Review Board reviewed and approved the protocol that was conducted in accordance with the Declaration of Helsinki and supervised by an Independent Data Monitoring Committee (IDMC).

Procedure and treatment

Patients were randomized to receive either 6 cycles of docetaxel 75 mg/m² plus cyclophosphamide 600 mg/m² (TC) on day 1 every 21 days or 6 cycles of docetaxel 75 mg/m², anthracycline, and cyclophosphamide 500 mg/m² (TAC) on day 1 every 21 days. Either epirubicin 60 mg/m² or doxorubicin 50 mg/m² was considered as an anthracycline drug in this study. After surgery, any further chemotherapy was not administered, and all patients were recommended to receive adjuvant radiotherapy. For HER2-positive breast cancer patients, adjuvant trastuzumab treatment was not mandatory due to its cost and being not covered by insurance at that time. ER- and/or PR-positive patients were treated with anti-estrogen regimens according to the discretion of the treating physician.

Response and outcome

The primary endpoint pCR rate is defined as the absence of invasive tumor in the breast and axillary lymph nodes

samples. The secondary endpoints include clinical response, EFS, and overall survival (OS). EFS was calculated as the disease interval between breast cancer diagnosis and the documented disease progression, local and regional recurrences, distant metastasis, secondary malignant carcinoma, or death from any cause. OS was measured from the date of initial diagnosis to the date of the last follow-up or death. Patients were followed up at 3-month intervals during the initial 2 years post-surgery and then at 6-month intervals for the next 3 years.

Statistical analysis

NATT was a phase III, non-inferiority study, designed to compare the efficacy of TC with TAC regimen in the neoadjuvant treatment of TNBC or HER2-positive breast cancer. The 96 enrolled patients were subjected to the Bayesian predictive probability method, suggested by IDMC, to test the possibility of inferior prognosis in TC arm due to its relatively high disease progression or recurrence. This outcome leads to the early stop of enrollments in the study on May 31, 2012, with a median follow-up period of 20 months. The details of the study design modification and statistical considerations were described in our previous report. In the present study, a longer period of follow-up was achieved to calculate the prognosis difference. Kaplan-Meier method was used to calculate the relationship between survival data and the potential influencing factors, such as age, menopausal status, body mass index (BMI), clinical tumor size stage, clinical lymph node stage, ER status, PR status, molecular subtype status, treatment regimens, and pCR status. Next, the factors associated with disease prognosis by log-rank tests were included to calculate the hazard ratio (HR) using the Cox proportional hazards model. HR was presented with their 95% confidence intervals (95% CI). All statistical analyses were performed by IBM SPSS Statistics (Version 20.0; IBM Corp., New York, USA) with a two-sided test at a 5% level of significance.

Results

Patient characteristics and treatment

The principal clinical and pathological characteristics were well-balanced between the two treatment arms, which have been described previously (Table 1). Between May 2009 and December 2011, a cohort of 96 patients was enrolled for the current data analysis, of whom 51 received TAC and 45

received TC treatment. The median age was 48.5 years old in the whole population. Fifty-six (58.3%) patients were diagnosed with stage III disease, and 80 (83.3%) patients had clinically positive lymph nodes. Forty-nine patients showed TNBC and 47 cases HER2-positive breast cancer.

Forty-nine (96.1%) patients were administrated with epirubicin as anthracycline agent. A significant difference in the treatment cycles and dose intensity was not observed between the two arms. After the neoadjuvant treatment and surgery, pCR rate inclined higher in the TAC group than in the TC arm (17.6% *vs.* 6.8%, $P=0.113$). The major severe side effects included hematologic toxicities in either group during the neoadjuvant treatment, and the patients recovered well during the long-term follow-up.

Event-free survival outcome

At data cut-off (August 31, 2015), the median follow-up was 52.9 [interquartile range (IQR), 33.7–61.7] months. Fourteen patients received the adjuvant trastuzumab treatment after surgery: 7 cases in each arm. Forty-four patients were recorded to show disease progression, recurrence, or death. Of the 13 patients that had disease progression during the neoadjuvant chemotherapy, 2 patients were diagnosed with contralateral supraclavicular lymph node metastasis and 1 patient was found with bone metastasis. Table 2 shows the disease outcomes according to the neoadjuvant treatment regimens. The events of EFS were found in 28 (62.2%) patients in the TC group, and 16 (31.4%) patients in the TAC group. Eight (15.7%) and 17 (37.8%) patients were diagnosed with distant metastasis in TAC and TC groups, respectively. TNBC or HER2-positive breast cancer patients who received TAC treatment displayed a better EFS than those treated with the TC regimen (HR, 0.39; 95% CI, 0.21–0.73; $P=0.002$). The estimated 5-year EFS was 66.1% and 29.8% for patients in the TAC and TC groups, respectively, which shows the sustained EFS advantage of adding anthracycline to TC regimen after a longer period of follow-up (Figure 1A). Regarding different molecular subtypes, TAC treatment achieved a better prognosis compared with the TC treatment in TNBC patients ($P=0.014$, Figure 1B). While in the HER2-positive subtype, 14 patients received adjuvant trastuzumab after surgery, and EFS trend was higher in the TAC arm than the TC arm ($P=0.091$, Figure 1C).

The univariable survival analysis, including age, menopausal status, BMI, clinical tumor size stage, clinical

Table 1 Characteristics of enrolled breast cancer patients

Characteristics	Case No.		P
	TAC (N=51)	TC (N=45)	
Age [mean (range)] (year)	47.2 (26–62)	48.0 (25–69)	0.204
≤35	4	5	
35–55	40	28	
>55	7	12	
BMI (kg/m ²)			0.723
≤25	39	33	
>25	12	12	
Menstrual status			0.428
Pre/peri-menopausal	30	30	
Postmenopausal	21	15	
Pathological Status			0.645
Invasive ductal carcinoma	45	41	
Others	6	4	
Tumor size stage			0.969
T ₀₋₂	24	21	
T ₃₋₄	27	24	
Lymph node stage			0.055
N0	12	4	
N+	39	41	
AJCC Stage			0.413*
IIB	24	15	
IIIA	21	25	
IIIB	5	3	
IIIC	1	2	
ER Status			0.267
Negative	45	36	
Positive	6	9	
PR Status			0.744
Negative	43	39	
Positive	8	6	
HER2 Status			0.990
Negative	26	23	
Positive	25	22	
Molecular subtypes			0.995
TNBC	26	23	
HR+/HER2+	11	10	
HR-/HER2+	14	12	
Adjuvant trastuzumab therapy			0.800
Yes	7	7	
No	44	38	

BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor-2; TNBC, triple-negative breast cancer; HR, hormonal receptor; *, P value was calculated by fisher's exact test.

Table 2 Disease outcome events by neoadjuvant chemotherapy regimens

Variables	n (%)	
	TAC (N=51)	TC (N=45)
Progression disease	4 (7.8)	9 (20.0)
Recurrence	12 (23.5)	22 (48.9)
Sites of recurrence		
Reginal	4 (7.8)	5 (11.1)
Distant	7 (13.7)	16 (35.6)
Reginal/Distant	1 (2.0)	1 (2.2)
Secondary cancer		
Breast cancer	1 (2.0)	0
Lung cancer	1 (2.0)	0
Ovarian cancer	0	1 (2.2)
Death without recurrence	0	1 (2.2)
Death with any cause	5 (9.8)	18 (40.0)
Total patients alive	46 (90.2)	27 (60.0)

lymph node stage, ER status, PR status, molecular subtype status, pCR status and trastuzumab usage, demonstrated that pCR status and clinical LN stage were associated with

EFS outcomes ($P=0.035$ and $P=0.034$, respectively). Patients that achieved pCR after neoadjuvant chemotherapy exhibited satisfactory EFS than those without pCR: the estimated 5-year EFS was 81.8% vs. 45.4% ($P=0.035$, *Figure 2A*). The multivariable analysis demonstrated that the neoadjuvant treatment regimen was an independent prognostic factor. After adjusting the factors of pCR status and clinical LN stage, TNBC or HER2-positive breast cancer patients treated with TAC had a superior EFS (HR, 0.48; 95% CI, 0.26–0.90; $P=0.021$).

Overall survival outcome

During the data cut-off with longer follow-up period, 23 patients perished and 21 were alive after disease progression or recurrence. Fewer deaths occurred in the TAC arm (5 cases) than in the TC (18 cases) (*Table 2*). The majority of deaths (95.7%) were due to disease recurrence/progression. Kaplan-Meier survival analysis showed that OS was in favor of the TAC treatment; the estimated 5-year OS was 88.4% in the TAC group and 51.6% in the TC group ($P<0.001$, *Figure 1D*). In TNBC patients, 18 deaths were recorded, and TAC neoadjuvant

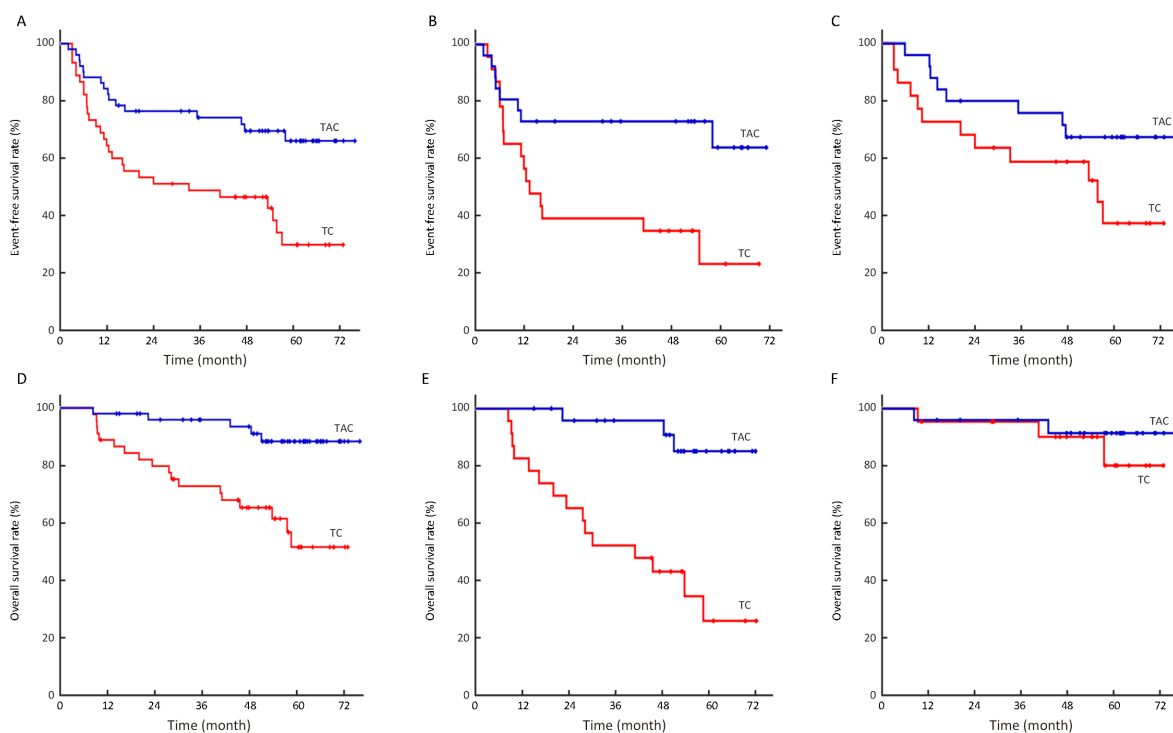


Figure 1 Kaplan-Meier plot of event-free survival (EFS) and overall survival (OS). (A) EFS in all patients ($P=0.002$); (B) EFS in triple negative breast cancer patients ($P=0.014$); (C) EFS in HER2-positive breast cancer patients ($P=0.091$); (D) OS in all patients ($P<0.001$); (E) OS in triple negative breast cancer patients ($P<0.001$); (F) OS in HER2-positive breast cancer patients ($P=0.478$).

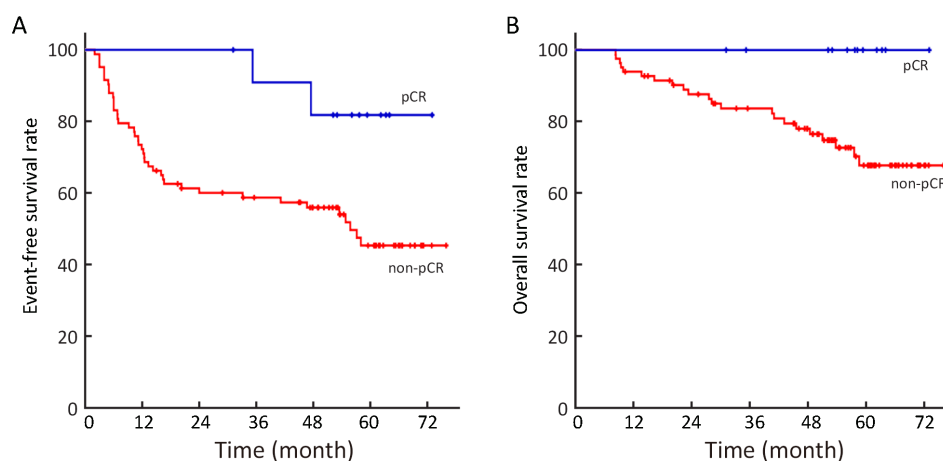


Figure 2 Kaplan-Meier plot of event-free survival (A) and overall survival (B) according to pathological complete remission (pCR) status ($P=0.035$ and $P=0.049$, respectively).

treatment was associated with a higher OS as compared to the TC treatment ($P<0.001$, *Figure 1E*). Five HER2-positive patients died, and cancer-specific survival at 5 years did not differ significantly between the two treatment arms ($P=0.478$, *Figure 1F*).

Any death occurrence was not observed in patients that achieved pCR after the neoadjuvant therapy. The estimated 5-year OS was 67.8% in patients without pCR, which was inferior to those achieved pCR after the neoadjuvant therapy ($P=0.049$, *Figure 2B*). In addition to the pCR status and treatment regimen, the univariable analysis also showed that the molecular subtype status was associated with OS ($P=0.002$). The multivariable analysis, including pCR status, molecular subtype status and treatment regimen, showed that the neoadjuvant treatment regimen and molecular subtype were independently associated with OS. The adjusted HR for OS was 0.20 (95% CI, 0.08–0.60; $P=0.003$), which was in favor of the TAC neoadjuvant treatment as compared with the TC treatment.

Discussion

After a median follow-up of 53 months, the NATT trial demonstrated a significant EFS and OS benefit from anthracycline-containing TAC neoadjuvant treatment in TNBC and HER2-positive breast cancer patients. In addition, the subgroup analysis showed that the TNBC patients could attain additional benefits from anthracycline-containing neoadjuvant treatment.

Our previous findings showed that TAC was superior to TC regimen regarding EFS with a median follow-up

period of 20 months, which led to the premature stop on the study recruitment (11). Consecutively, TAC treatment was numerically better than TC regimen in terms of OS. In the present study, the updated follow-up data demonstrated a sustained EFS benefit from the TAC treatment. Moreover, a total of 23 deaths were recorded, and the TAC neoadjuvant treatment was associated with a significantly improved OS than that for the TC therapy. The joint analysis of ABC trials demonstrated that taxanes plus AC regimens, including TAC, AC followed-up with weekly paclitaxel, or dose-dense paclitaxel, were associated with a better invasive disease-free survival (DFS) than that for the non-anthracycline-containing TC regimen. This result supported anthracycline utility in HER2-negative breast cancer treatment (12).

EBCTCG meta-analysis in 2012 found that 4 standard cycles of AC were equivalent to cyclophosphamide, methotrexate and 5-fluorouracil (CMF) therapy. On the other hand, the higher cumulative dosage of anthracycline could reduce breast cancer mortality as compared to CMF (5). A meta-analysis of Cancer and Leukemia Group B (CALGB) trials showed that ER-negative breast cancer derived more benefits from current adjuvant chemotherapy regimens than ER-positive tumors (13). Also, exploratory analysis from ABC trials found that the additional anthracycline treatment could reduce further disease recurrence in TNBC patients than in the luminal patients (12). In the current study, 18 deaths were recorded in the TNBC patients, which was higher than the HER2-positive patients. This feature may be attributed to the lack of target agents, aggressive biology behavior, and inadequate

treatment intensity in TNBC patients (11,14). Moreover, one subgroup of TNBC was immune-related disease and had higher tumor infiltrating lymphocytes, which were associated with a better disease outcome (15). A preclinical study demonstrated that the treatment with anthracycline agents could significantly induce host immunity reaction, which could inhibit the tumor proliferation (16). Our study found that the TNBC patients treated with TAC had superior EFS and OS compared with the TC therapy, indicating that anthracycline is essential for TNBC patients in a neoadjuvant setting.

Several studies have reported that HER2-positive breast cancer has been particularly sensitive to anthracycline treatment (7,8). The efficacy of trastuzumab as neoadjuvant or adjuvant therapy has been well-established in HER2-positive tumors (4). In a neoadjuvant setting, integrating chemotherapy and trastuzumab can significantly increase the pCR rate compared with chemotherapy alone (17). Dual HER2 blockade with additional lapatinib or pertuzumab treatment can further improve the pCR rate (18,19). Currently, chemotherapy plus trastuzumab and pertuzumab regimen has been approved by Food and Drug Administration (FDA) in a neoadjuvant treatment of HER2-positive breast cancer (20). With a median of a 10-year follow-up, Breast Cancer International Research Group (BCIRG) 006 study demonstrated that DFS was similar between TCH and ACTH treatment, supporting that anthracycline may be excluded on the basis of trastuzumab therapy for HER2-positive tumors (21). However, in this NATT study, wherein trastuzumab was not allowed in the neoadjuvant treatment, anthracycline-containing TAC regimen was associated with a trend of higher EFS than the TC treatment in HER2-positive breast cancer patients. OS was not significantly different between these two treatment arms. This phenomenon may potentially be explained by 14 patients receiving adjuvant trastuzumab treatment, a relatively small number of enrolled patients, and available effective anti-HER2 target agents for patients with metastatic disease (22).

In the neoadjuvant treatment, both Germany and FDA meta-analysis demonstrated that pCR could predict the survival outcome in TNBC or HER2-positive breast cancer patients (4,23). In this study, TNBC or HER2-positive breast cancer patients who achieved pCR had a significantly improved EFS and OS than those without pCR. NeOAdjuvant Herceptin (NOAH) study demonstrated that the doubled pCR rate with neoadjuvant trastuzumab treatment can translate into EFS benefit in HER2-positive

tumors (17). For TNBC patients, adding carboplatin to anthracycline- and taxane-containing regimen significantly improved the pCR rate (24), which was also associated with numerically higher EFS (25). Findings from our previous NATT study showed that the pCR rate difference was not apparent between the TAC and TC treatment, whereas additional disease progressions were observed during neoadjuvant therapy in the TC group. Retrospective data showed that TNBC with residual disease after neoadjuvant chemotherapy exhibited worse DFS compared with the other breast cancer subtypes (26). In the current study, the updated follow-up data demonstrated not only a sustained EFS benefit but also a better OS outcome from additional anthracycline treatment, especially in TNBC patients. This feature may arise from a relatively low pCR rate and more patients with residual diseases after neoadjuvant chemotherapy in this cohort of patients.

Conclusions

With a median follow-up period of 53 months, anthracycline-containing TAC neoadjuvant treatment had a sustained EFS benefit and a better OS compared with the TC treatment in TNBC and HER2-positive breast cancer patients. This updated follow-up results postulate that anthracycline should be considered as a necessary and effective drug in this trial setting, especially in TNBC patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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