Breast Cancer Research and Treatment (2019) 175:659–666
https://doi.org/10.1007/s10549-019-05207-x

CLINICAL TRIAL

Efficacy and safety of taxane plus anthracycline with or without cyclophosphamide in Chinese node-positive breast cancer patients: an open-label, randomized controlled trial

Yan Lin[1] · Changjun Wang[1] · Xin Huang[1] · Xingtong Zhou[1] · Yidong Zhou[1] · Feng Mao[1] · Jinghong Guan[1] · Yu Song[1] · Ying Zhong[1] · Ying Xu[1] · Qiang Sun[1]

Received: 9 January 2019 / Accepted: 16 March 2019 / Published online: 1 April 2019

Abstract

Purpose To evaluate and compare the efficacy and safety of the taxane plus anthracycline (TA) regimen vs. the taxane plus anthracycline plus cyclophosphamide (TAC) regimen as adjuvant chemotherapy in Chinese patients with node-positive breast cancer (BCa).

Methods Patients with BCa ($n=640$) were recruited between January 2010 and June 2012. All patients were randomized to receive six cycles of adjuvant therapy with the TA or TAC regimen. The primary endpoint was disease-free survival (DFS). The secondary endpoints were overall survival (OS), quality of life (QoL), and chemotherapy-related toxicity. Finally, 630 patients were evaluable, with a median follow-up of 70 months.

Results There were no differences in the 70-month median DFS and OS between the two groups (DFS: TA 79.7% vs. TAC 75.6%, $P=0.371$; OS: TA vs. TAC, 85.1% vs. 87.6%, $P=0.271$). The TA group had lower frequencies grade III/IV vomiting (TA vs. TAC, 11.7% vs. 18.1%, $P=0.025$) and nausea (13.0% vs. 19.4%, $P=0.031$). The health-related QoL score was higher in the TA group (74.1 ± 5.3 vs. 67.9 ± 4.4, $P=0.001$ vs. TAC).

Conclusions In the adjuvant setting, compared with the TAC regimen, the TA regimen exhibits no significant difference with respect to DFS and OS in Chinese patients with node-positive BCa. On the other hand, TA is associated with less severe adverse events, lower economic burden, and better QoL.

Keywords Breast cancer · Adjuvant chemotherapy · Efficacy · Safety · Quality of life · Randomized controlled study

Abbreviations

BCa	Breast cancer
CINV	Chemotherapy-induced nausea and vomiting
DFS	Disease-free survival
NSABP	National Surgical Adjuvant Breast and Bowel Project
OS	Overall survival
QoL	Quality of life
TA	Taxane and anthracycline
TAC	Taxane plus anthracycline with cyclophosphamide

Introduction

Breast cancer (BCa) is the leading malignancy prevailing in women worldwide [1]. Adjuvant chemotherapy is considered as a standard therapeutic option that improves disease-free survival (DFS) and overall survival (OS), especially in high-risk patient subgroups such as node-positive BCa [2].

The use of regimens containing a taxane and an anthracycline has been shown to be superior to a regimen containing an anthracycline and cyclophosphamide [3–5] and such regimens are well recognized by the guidelines for the treatment of node-positive BCa [6, 7]. Nevertheless, most of the clinical trials that led to these guidelines focused on the administration of these agents, i.e. on the dosage and whether in combination or sequentially [8]. Few studies have questioned the necessity of combining cyclophosphamide with a taxane and an anthracycline in the adjuvant setting for node-positive BCa.

✉ Qiang Sun
pumclinyan@163.com

[1] Department of Breast Disease, Peking Union Medical College Hospital, Peking Union Medical College, 1 Shuaifuyuan, Wangfujing, Beijing 100730, China

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-30 trial compared the efficacy of three adjuvant chemotherapy regimens in patients with early-stage, node-positive BCa: (1) doxorubicin plus cyclophosphamide followed by docetaxel (AC→T); (2) concurrent TAC; and (3) TA [9]. The results revealed that TA was not inferior to TAC in terms of overall survival (OS) and was associated with less toxicity [9]. Unfortunately, no other large clinical trial examined the TA vs. TAC regimens [4, 6].

Besides survival, treatment tolerability and quality of life (QoL) remain central concerns in clinical practice. Chemotherapy-induced nausea and vomiting (CINV) is one of the most distressing problems experienced by the patients [10]. It can severely impair the patients' QoL, compromise cognitive functions and physical ability, and may result in discontinuation of treatment [11]. Cyclophosphamide is considered as highly emetogenic and is a particularly high risk factor for CINV [12, 13].

Therefore, the question is whether TA regimens could be used for node-positive BCa patients, without compromise regarding the oncologic outcomes, but with less adverse effects. Hence, the present randomized controlled study aimed to compared the efficacy, safety, and 6-year survival of the TA versus TAC regimens in Chinese patients with node-positive BCa with respect to OS, DFS, treatment-related adverse events, and QoL.

Patients and methods

Patients

The study protocol was approved by the Institutional Review Board of Peking Union Medical College in accordance with the latest version of the Declaration of Helsinki. Female BCa patients ($n = 640$) were prospectively enrolled for adjuvant chemotherapy between January 2010 and June 2012. All patients provided written informed consent before participation in the study. Patient safety was monitored by an independent data safety monitoring committee. This trial was registered with ClinicalTrials.gov (#NCT02838225).

The inclusion criteria were: (1) 18–70 years of age at diagnosis; (2) diagnosed with histologically confirmed invasive BCa; (3) stage pT1-4N1-3M0 (i.e., positive axillary node and no distant metastasis); (4) received breast-conserving surgery or modified mastectomy; (5) Eastern Cooperative Oncology Group (ECOG) status 0–1 [14]; (6) left ventricular ejection fraction ≥ 50%; (7) normal hematologic, hepatic, and renal functions; and (8) for women of child-bearing potential, willing to use a validated contraceptive medication or device during the whole study period. The exclusion criteria were: (1) BCa without axillary node metastases, inflammatory BCa, metastatic BCa, or bilateral BCa; (2) serious complications such as cardiopulmonary, hepatorenal, or coagulation conditions; (3) history of chemotherapy or radiation therapy; or (4) pregnant or lactating women.

Study design and chemotherapy regimens

All eligible patients were randomized 1:1 to receive six cycles of adjuvant chemotherapy with open-label TA or TAC regimen. Randomization was performed using a central computer system by permutated blocks of a randomly varying size.

The TA regimen was given intravenously every 21 days and included epirubicin (Pfizer Pharmaceuticals Inc., Shanghai, China) 75 mg/m^2 on day 1 plus docetaxel (Sanofi-Aventis Pharmaceuticals Ltd., Shanghai, China) 75 mg/m^2 on day 1. The TAC regimen was given every 21 days and included intravenous (day 1) epirubicin 75 mg/m^2, docetaxel 75 mg/m^2, and cyclophosphamide 500 mg/m^2 (SL Pharmaceutical Co., Ltd, Beijing, China).

To prevent chemotherapy-induced toxic effects, all patients received 8 mg of ondansetron (5-hydroxytryptamine-3 receptor antagonist; Qilu Pharmaceutical Co., Ltd., Jinan, China) intravenously on day 1 for antiemesis, and 3 days of 45 mg of oral dexamethasone for prophylaxis of anaphylactic reaction [15]. Hematologic, clinical biochemistry, serologic, and virologic assays were performed before chemotherapy and repeated weekly during follow-up. Subcutaneous injection of granulocyte colony-stimulating factor (G-CSF) was given to any patient with neutrophil count below 500/μL or experiencing febrile neutropenia [16]. Other adjuvant therapies such as endocrine therapy, radiotherapy, and trastuzumab were given according to the NCCN guidelines [6].

Follow-up evaluations

All patients were followed by an independent research physician at the outpatient clinic and who was blinded to grouping. Chest X-ray, blood tumor biomarkers, and radiological examinations such as breast and abdomen ultrasound were performed every 6 months for the first 2 years and every 12 months afterwards. Bone scan was performed each year.

Primary and secondary endpoints

The primary efficacy endpoint was DFS, which was defined as the time from randomization until first relapse (local, regional, or distant), contralateral BCa, or death from any cause. The secondary endpoints were OS, QOL, and chemotherapy-related toxicities. OS was defined as the time from randomization to death from any cause. Treatment-related adverse events were evaluated using the National Cancer

Institute Common Toxicity Criteria Grading version 4.0.A [17]. Health-related QoL was assessed on day 21 of the sixth cycle of chemotherapy in a self-reported manner using a validated Chinese translation of the European Organization for Research and Treatment in Cancer Quality of Life Questionnaire (EORTC QLQ-C30). This questionnaire involves global health, physical, role, social, emotional, and cognitive functioning dimensions, with a higher score indicating a better QoL [18].

Statistical analysis

The present study adopted a hybrid design described by Freidlin et al. [19]. Considering 80% power, 0.025 one-sided significance level, 30-month accrual, 70-month follow-up, and 10% dropout rate, the sample size was set at 614 patients.

SPSS 19.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Continuous data are expressed as means ± standard deviation and were compared using the independent Student's t test. Categorical data are expressed as n (%) and were compared using the Fisher exact test. DFS and OS were evaluated with the Kaplan–Meier method and were analyzed using the log-rank test. A two-tailed P value of less than 0.05 was considered to be statistically significant.

Results

Baseline patient characteristics

During the study period, 640 Chinese patients with node-positive BCa were enrolled and randomized to TA ($n=320$) or TAC ($n=320$) (Fig. 1). Two patients withdrew consent and quit the study before randomization. Baseline clinicopathological characteristics are shown in Table 1. The two treatment arms were comparable with respect to age, menopause, tumor staging, proliferation index, lymph node staging, ER/PR positivity, HER2 status, and type of operation (all $P>0.05$).

DFS and OS

All patients were followed for 62–91 months (median, 70 months). Two patients dropped out during follow-up. Overall, 35 patients had local recurrence as the first event (TA 16; TAC 19) and 74 had distant metastasis (bone metastasis: TA 10, TAC 11; lung metastasis: TA 12, TAC 14; liver metastasis: TA 9, TAC 12; brain metastasis: TA 3, TAC 3), and multiple metastasis (TA 14, TAC 18) as the first event. Salvage surgical resection and radiation therapy were performed for patients with recurrent chest wall disease. Combination of radiation therapy and systemic

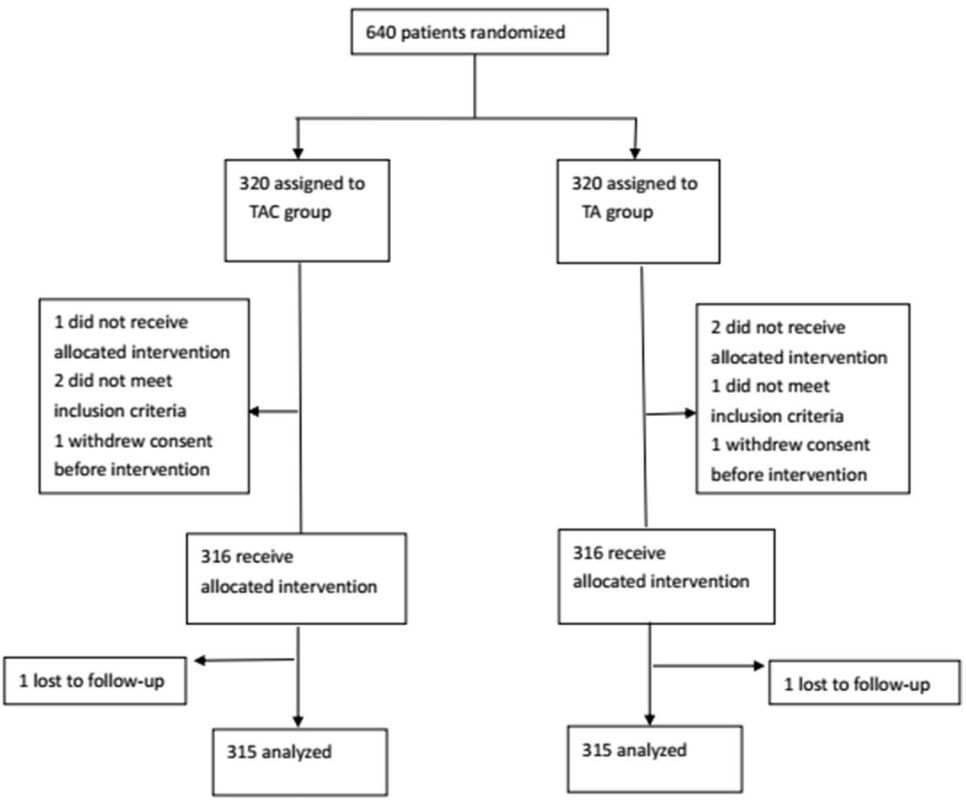

Fig. 1 Patient allocation flow chart

Table 1 Baseline characteristics of node-positive BCa patients ($n=630$)

	TA group ($n=315$)	TAC group ($n=315$)	P value
Age, year, mean (range)	51.2 (33–69)	50.8 (30–68)	0.521
Post-menopause, *n* (%)	142 (45.1%)	139 (44.1%)	1.000
Tumor staging, *n* (%)			0.213
T 1	21 (6.7)	25 (7.9)	
T 2	103 (32.7)	103 (32.7)	
T 3	179 (56.8)	177 (56.2)	
T 4	12 (3.8)	10 (3.2)	
Proliferation index, *n* (%)			0.199
Grade 1	47 (14.9)	44 (14.0)	
Grade 2	143 (45.4)	150 (47.6)	
Grade 3	125 (39.7)	121 (38.4)	
Lymph node staging, *n* (%)			0.199
N 1	78 (24.8)	75 (23.8)	
N 2	133 (42.2)	134 (42.5)	
N 3	104 (33.0)	106 (33.7)	
ER/PR positivity, *n* (%)	170 (54.0)	167 (53.0)	1.000
HER2 status, *n* (%)			1.000
0–2	239 (75.9)	247 (78.4)	
3+	76 (24.1)	68 (21.6)	
Type of operation, *n* (%)			1.000
Breast preservation	47 (14.9)	45 (14.3)	
Modified mastectomy	268 (85.1)	270 (85.7)	

chemotherapy was given to patients with supraclavicular node recurrence. Bisphosphonate therapy was initiated to control bone metastasis. Intravenous chemotherapy was given to patients with visceral crisis for salvage therapy. Overall, 47 patients died in the TA group and 39 patients died in the TAC group. There were no differences in OS and DFS (OS: TA vs. TAC, 97.1% vs. 96.4%, $P=0.965$; DFS: 93.6% vs. 92.9%, $P=0.761$) between the two groups during the 6-year follow-up (Fig. 2).

Chemotherapy-related toxicity

Grade III–IV chemotherapy-related toxicities are shown in Table 2. Compared with TAC, the TA regimen was associated with significantly lower frequencies of grade III–IV vomiting (TA vs. TAC, 11.7% vs. 18.1%, $P=0.025$) and grade III–IV nausea (TA vs. TAC 13.0% vs. 19.4%, $P=0.031$), while the two treatment arms showed similar frequencies of patients experiencing grade III–IV peripheral neuropathy (TA vs. TAC, 5.1% vs. 8.3%, $P=0.110$) and grade III–IV neutropenia (8.9% vs. 12.4%, $P=0.155$). The two groups also showed no significant difference in diarrhea (TA vs. TAC, 4.4% vs. 4.8%, $P=0.849$). No grade III–IV alopecia or cardiac events occurred.

Health-related QoL

Health-related QoL data are shown in Table 3. There was significant difference in Global health status score between TA and TAC groups (TA vs. TAC, 74.11 ± 5.250 vs. 67.92 ± 4.449, $P=0.001$). With respect to QoL subdomains, the TA regimen was associated with significantly better physical functions (TA vs. TAC, 80.27 ± 5.388 vs. 79.08 ± 6.871, $P=0.045$), role functions (75.12 ± 6.813 vs. 73.38 ± 5.451, $P=0.001$) and emotional functions (78.06 ± 5.152 vs. 76.95 ± 7.591, $P=0.032$). Neither of the groups showed QoL superiority in social and cognitive functioning domains (all P values >0.05).

Discussion

No gold standard treatment has been established as an adjuvant chemotherapy regimen for patients with node-positive BCa. The NCCN guidelines only categorize chemotherapy regimens into ‘preferred’ and ‘other’, and recommend the same regimen for adjuvant and neoadjuvant therapies [6]. Although the TA regimen was widely used in the neoadjuvant setting [20], it has been rarely applied as adjuvant therapy. In patients with metastatic disease, the TA regimen already showed an efficacious advantage [21]. The trials

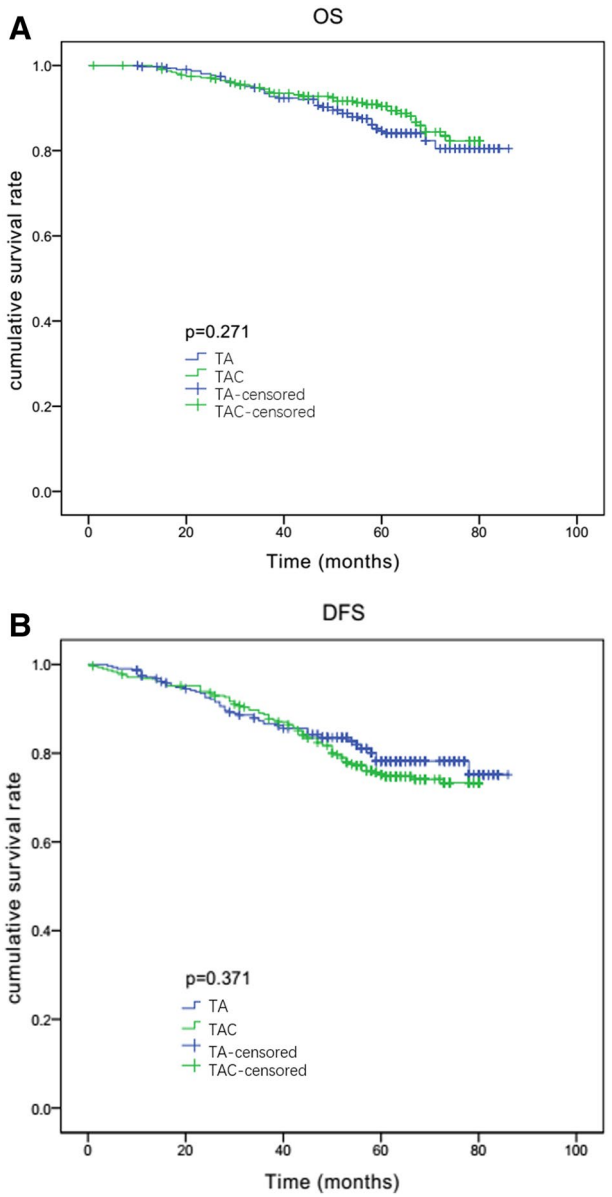

Fig. 2 6-year DFS and OS curves of TA regimen vs. TAC regimen

performed by the Eastern Cooperative Oncology Group (ECOG) showed that the response rates of TA were 57% (E1196) [22], and 46% (E1193) [23]. Thus, the TA regimen as an adjuvant therapy warrants further evaluation. The present study demonstrated that the TA and TAC regimens had comparable DFS and OS in the adjuvant setting over a follow-up period of up to 70 months. In addition, TA was associated with less toxicity in terms of vomiting and nausea.

The TAC regimen is widely used in the adjuvant setting and has been validated by several clinical trials [24–28]. On the other hand, the TA regimen is not recommended by the guidelines due to the lack of robust evidence regarding its efficacy [6, 7]. The NSABP B30 trial suggested that TA was not inferior to TAC [9], but the dosage used in this trial was higher in the AC-T regimen (T 100 mg/m^2) than in the TA/TAC regimens (T 75 mg/m^2). Even if the trial aimed to compare the three regimens, the doses of the same drug were not balanced among the regimens. Thus, the present study was designed to directly assess the efficacy of the TA regimen in the adjuvant setting and also evaluated its effect in high-risk patients with BCa. To the best of our knowledge, the present work is the first trial regarding the TA regimen as adjuvant chemotherapy for Chinese patients with node-positive BCa. The study revealed that adding cyclophosphamide to a regimen containing a taxane and an anthracycline did not lead to significant improvement in DFS of patients with node-positive BCa. Despite the differences in taxane dosage, this result is supported by the NSABP B30 trial. Taken together, the results further support the notion that a de-escalating strategy in TAC regimen with the omission of cyclophosphamide does not significantly compromise the efficacy. These results are of importance in the current era of chemotherapy de-escalation and individualized medicine [29, 30].

The North American Breast Cancer Intergroup Trial ECOG E2197 trial tried to identify the effectiveness of TA as an adjuvant treatment. The trial revealed that TA showed no survival advantage over AC for patients with node-positive BCa [5]. It also raised the concern that TA had limited effect on node-positive BCa and hence could not serve as a substitution for intensive regimens such as TAC. But this trial recruited patients with 0–3 positive lymph nodes, and patients with node-negative BCa accounted for 66%. Hence, the superiority of TA on survival could probably be undermined by the large proportion of lower-risk (node-negative) patients enrolled. In addition, in the pre-specified subgroup analysis according to ER and PR expression levels, the high-risk ER/PR-negative patients showed improving trends of DFS with TA.

Another key issue of the TA and TAC regimens is safety. Severe adverse effects could undermine the patients' tolerability and QoL, resulting in treatment discontinuation [31]. The present study demonstrated that TA had a more acceptable profile of adverse events with less vomiting and nausea. Serious vomiting is one of the most unfavorable side effects in patients receiving chemotherapy. Our results showed that patients receiving TA regimen showed reduced frequency of grade III–IV vomiting and nausea compared to the TAC regimen. The two regimens had similar frequency of grade III–IV peripheral neuropathy. Given that cyclophosphamide has definite emetogenic risk [32], the improved safety profile of TA could largely be attributed to the absence of cyclophosphamide.

Furthermore, there are several debates on the administration of cyclophosphamide due to the risks of hemorrhagic cystitis and amenorrhea [33, 34]. Especially for pre-menopausal women, gonadotoxicity could be a big

Table 2 Chemotherapy-induced toxicities (Grade 3 or 4), *n* [%]

	TA		TAC		X^2	*P*
	No.	Rate (%)	No.	Rate (%)		
Vomiting					5.002	0.025
No	278	88.3	258	81.9		
Yes	37	11.7	57	18.1		
Nausea					4.679	0.031
No	274	87.0	254	80.6		
Yes	41	13.0	61	19.4		
Diarrhea					0.036	0.849
No	301	95.6	300	95.2		
Yes	14	4.4	15	4.8		
Peripheral neuropathy					2.551	0.110
No	299	94.9	289	91.7		
Yes	16	5.1	26	8.3		
Neutropenia					2.021	0.155
No	287	91.1	276	87.6		
Yes	28	8.9	39	12.4		

Table 3 Health-related QoL (means ± SD)

	TA group ($n=315$)	TAC group ($n=315$)	*P* value
Global health	74.11 ± 5.250	67.92 ± 4.449	0.001
Physical functions	80.27 ± 5.388	79.08 ± 6.871	0.016
Role	75.12 ± 6.813	73.38 ± 5.451	0.025
Emotional	78.06 ± 5.152	76.95 ± 7.591	0.358
Cognitive	78.08 ± 5.378	77.84 ± 5.309	0. 576
Social	77.63 ± 5.278	77.32 ± 5.107	0.022

concern when considering chemotherapy. Consequently, the removal of cyclophosphamide could partially mitigate chemotherapy-induced amenorrhea and protect ovarian function. In addition, from a socioeconomic point of view, the removal of cyclophosphamide lowers the cost of chemotherapy and improves treatment accessibility.

Besides long-term survival, QoL is a key outcome that has a significant effect on the general health and wellbeing of BCa patients. High QoL shows a positive correlation with cancer patients' survival [35]. The present results showed that the TA regimen was associated with a significantly better QoL, especially with respect to physical, role, and emotional functions. These results could probably be explained by more frequent serious vomiting due to the TAC regimen might restrict the patients' daily activities, requiring more medical interventions. Second, the addition of cyclophosphamide could increase the time needed for drug administration and prolonged patients' immobilization time, which is associated with more restrictions in patient's role and physical functions.

The present study has some limitations. This study was not designed for subgroup analyses based on stratification of risk factors such as age and hormone receptor status. Nevertheless, the present study was the first randomized controlled study offering the highest level of evidence regarding the TA and TAC regimens as adjuvant chemotherapy in patients with node-positive BCa. Second, a 6-year follow-up period is short when considering the relatively long survival of patients with breast cancer. Hence, long-term follow-up is presently ongoing and data will be available in some years. Third, the psychometric test results are subjected to multiple confounding effects, including the patient characteristics, investigator bias, and measurement variation. The QoL measurement was performed in a self-reported manner by patients and the individual who collected the data was blind to patient grouping.

In conclusion, our results showed that there were no differences in OS and DFS between six cycles of TA vs. six cycles of TAC as adjuvant chemotherapy for patients with node-positive BCa. The TA regimen is associated with lower frequencies of chemotherapy-induced serious vomiting and nausea, and better QoL when compared with the TAC regimen. Due to its comparable efficacy, better QoL, and relative superiority in toxicities, the TA regimen can be considered as a reasonable treatment option as an adjuvant chemotherapy for node-positive BCa. In the era of chemotherapy de-escalation and individualized medicine, avoiding the use of cyclophosphamide could be of clinical and socioeconomic significance for the treatment of BCa.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent All patients provided written informed consent forms before participation in the study.

Research involving human participants The study protocol was approved by the Institutional Review Board at Peking Union Medical College in accordance with the latest version of the Declaration of Helsinki. This trial was registered with ClinicalTrials.gov (#NCT02838225).

References

1. Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. CA: Cancer J Clin 67(1):7–30. https://doi.org/10.3322/caac.21387
2. Schmidt M, Koelbl H (2012) Adjuvant chemotherapy in early breast cancer. Minerva Ginecol 64(1):53–65
3. Nabholtz JM, Riva A (2001) Taxane/anthracycline combinations: setting a new standard in breast cancer? The Oncologist 6(Suppl 3):5–12
4. Saurel CA, Patel TA, Perez EA (2010) Changes to adjuvant systemic therapy in breast cancer: a decade in review. Clin Breast Cancer 10(3):196–208. https://doi.org/10.3816/CBC.2010.n.027
5. Goldstein LJ, O'Neill A, Sparano JA, Perez EA, Shulman LN, Martino S, Davidson NE (2008) Concurrent doxorubicin plus docetaxel is not more effective than concurrent doxorubicin plus cyclophosphamide in operable breast cancer with 0 to 3 positive axillary nodes: North American Breast Cancer Intergroup Trial E 2197. J Clin Oncol 26(25):4092–4099. https://doi.org/10.1200/JCO.2008.16.7841
6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast cancer. Version 4.2018 (2019). National Comprehensive Cancer Network, Fort Washington
7. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, Zackrisson S, Cardoso F, Committee EG (2015) Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 26(Suppl 5):v8–30. https://doi.org/10.1093/annonc/mdv298
8. Denduluri N, Somerfield MR, Eisen A, Holloway JN, Hurria A, King TA, Lyman GH, Partridge AH, Telli ML, Trudeau ME, Wolff AC (2016) Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2)-negative and adjuvant targeted therapy for HER2-positive breast cancers: an American Society of Clinical Oncology Guideline Adaptation of the Cancer Care Ontario Clinical Practice Guideline. J Clin Oncol 34(20):2416–2427. https://doi.org/10.1200/JCO.2016.67.0182
9. Ganz P, Land S, Geyer C, Costantino J, Pajon E, Fehrenbacher L, Atkins J, Polikoff J, Vogel V (2008) Erban J NSABP B-30: definitive analysis of quality of life (QOL) and menstrual history outcomes from a randomized trial evaluating different women with operable, node-positive breast cancer. In: Presented at the 31st annual San Antonio Breast Cancer Symposium, December 10–14, 2008. Abstract
10. Fernandez-Ortega P, Caloto MT, Chirveches E, Marquilles R, Francisco JS, Quesada A, Suarez C, Zorrilla I, Gomez J, Zabaleta P, Nocea G, Llombart-Cussac A (2012) Chemotherapy-induced nausea and vomiting in clinical practice: impact on patients' quality of life. Support Care Cancer 20(12):3141–3148. https://doi.org/10.1007/s00520-012-1448-1
11. Grunberg SM (2009) Obstacles to the implementation of antiemetic guidelines. J Natl Compr Cancer Netw 7(5):601–605
12. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, Chesney M, Clark-Snow RA, Flaherty AM, Freundlich B, Morrow G, Rao KV, Schwartz RN, Lyman GH, American Society of Clinical O (2011) Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 29(31):4189–4198. https://doi.org/10.1200/JCO.2010.34.4614
13. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, Bria E, Clark-Snow RA, Espersen BT, Feyer P, Grunberg SM, Hesketh PJ, Jordan K, Kris MG, Maranzano E, Molassiotis A, Morrow G, Olver I, Rapoport BL, Rittenberg C, Saito M, Tonato M, Warr D, Group EMGW (2010) Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol 21(Suppl 5):v232–v243. https://doi.org/10.1093/annonc/mdq194
14. Sloan JA, Frost MH, Berzon R, Dueck A, Guyatt G, Moinpour C, Sprangers M, Ferrans C, Cella D, Clinical Significance Consensus Meeting G (2006) The clinical significance of quality of life assessments in oncology: a summary for clinicians. Support Care Cancer 14(10):988–998. https://doi.org/10.1007/s00520-006-0085-y
15. Jacobs C, Hutton B, Mazzarello S, Smith S, Joy A, Amir E, Ibrahim MF, Gregario N, Daigle K, Eggert L, Clemons M (2015) Optimisation of steroid prophylaxis schedules in breast cancer patients receiving docetaxel chemotherapy-a survey of health care providers and patients. Support Care Cancer 23(11):3269–3275. https://doi.org/10.1007/s00520-015-2731-8
16. Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leighl NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO, American Society of Clinical O (2015) Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline update. J Clin Oncol 33(28):3199–3212. https://doi.org/10.1200/JCO.2015.62.3488
17. Lemieux J, Goodwin PJ, Bordeleau LJ, Lauzier S, Theberge V (2011) Quality-of-life measurement in randomized clinical trials in breast cancer: an updated systematic review (2001–2009). J Natl Cancer Inst 103(3):178–231. https://doi.org/10.1093/jnci/djq508
18. Montazeri A (2009) Quality of life data as prognostic indicators of survival in cancer patients: an overview of the literature from 1982 to 2008. Health Quality Life Outcomes 7:102. https://doi.org/10.1186/1477-7525-7-102
19. Freidlin B, Korn EL, George SL, Gray R (2007) Randomized clinical trial design for assessing noninferiority when superiority is expected. J Clin Oncol 25(31):5019–5023. https://doi.org/10.1200/JCO.2007.11.8711
20. Yang H, Zhou L, Wang S, Cao Y, Tong F, Liu P, Zhou B, Cheng L, Liu M, Liu H, Xie F, Guo J, Wang S, Peng Y (2018) Retrospective analysis of concurrent docetaxel and epirubicin neoadjuvant versus adjuvant chemotherapy: which leads to better outcomes for different subtype breast cancer patients? Medicine 97(40):e12690. https://doi.org/10.1097/MD.0000000000012690
21. Radaideh SM, Sledge GW (2008) Taxane vs. taxane: is the duel at an end? A commentary on a phase-III trial of doxorubicin and docetaxel versus doxorubicin and paclitaxel in metastatic breast cancer: results of the ERASME 3 study. Breast Cancer Res Treat 111(2):203–208. https://doi.org/10.1007/s10549-007-9776-4
22. Sparano JA, O'Neill A, Schaefer PL, Falkson CI, Wood WC (2000) Phase II trial of doxorubicin and docetaxel plus granulocyte colony-stimulating factor in metastatic breast cancer: Eastern Cooperative Oncology Group Study E1196. J Clin Oncol 18(12):2369–2377. https://doi.org/10.1200/JCO.2000.18.12.2369

23. Sledge GW, Neuberg D, Bernardo P, Ingle JN, Martino S, Rowinsky EK, Wood WC (2003) Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as frontline chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol 21(4):588–592. https://doi.org/10.1200/JCO.2003.08.013
24. Nowak AK, Wilcken NR, Stockler MR, Hamilton A, Ghersi D (2004) Systematic review of taxane-containing versus non-taxane-containing regimens for adjuvant and neoadjuvant treatment of early breast cancer. Lancet Oncol 5(6):372–380. https://doi.org/10.1016/S1470-2045(04)01494-9
25. Bria E, Nistico C, Cuppone F, Carlini P, Ciccarese M, Milella M, Natoli G, Terzoli E, Cognetti F, Giannarelli D (2006) Benefit of taxanes as adjuvant chemotherapy for early breast cancer: pooled analysis of 15,500 patients. Cancer 106(11):2337–2344. https://doi.org/10.1002/cncr.21886
26. Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A (2007) Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation. Health Technol Assess 11(40):1–144
27. Curigliano G, Criscitiello C (2017) Maximizing the clinical benefit of anthracyclines in addition to taxanes in the adjuvant treatment of early breast cancer. J Clin Oncol 35(23):2600–2603. https://doi.org/10.1200/JCO.2017.72.5960
28. De Laurentiis M, Cancello G, D'Agostino D, Giuliano M, Giordano A, Montagna E, Lauria R, Forestieri V, Esposito A, Silvestro L, Pennacchio R, Criscitiello C, Montanino A, Limite G, Bianco AR, De Placido S (2008) Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. J Clin Oncol 26(1):44–53. https://doi.org/10.1200/JCO.2007.11.3787
29. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, Geyer CE Jr, Dees EC, Goetz MP, Olson JA Jr, Lively T, Badve SS, Saphner TJ, Wagner LI, Whelan TJ, Ellis MJ, Paik S, Wood WC, Ravdin PM, Keane MM, Gomez Moreno HL, Reddy PS, Goggins TF, Mayer IA, Brufsky AM, Toppmeyer DL, Kaklamani VG, Berenberg JL, Abrams J, Sledge GW, Jr. (2018) Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 379(2):111–121. https://doi.org/10.1056/NEJMoa1804710
30. Harbeck N, Gluz O, Christgen M, Kates RE, Braun M, Kuemmel S, Schumacher C, Potenberg J, Kraemer S, Kleine-Tebbe A, Augustin D, Aktas B, Forstbauer H, Tio J, von Schumann R, Liedtke C, Grischke EM, Schumacher J, Wuerstlein R, Kreipe HH, Nitz UA (2017) De-escalation strategies in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (BC): final analysis of the West German Study Group adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early BC HER2- and hormone receptor-positive phase II randomized trial-efficacy, safety, and predictive markers for 12 weeks of neoadjuvant trastuzumab emtansine with or without endocrine therapy (ET) versus trastuzumab plus ET. J Clin Oncol 35 (26):3046–3054. https://doi.org/10.1200/JCO.2016.71.9815
31. Montazeri A (2008) Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. J Exp Clin Cancer Res 27:32. https://doi.org/10.1186/1756-9966-27-32
32. Warr D (2012) Management of highly emetogenic chemotherapy. Curr Opin Oncol 24(4):371–375. https://doi.org/10.1097/CCO.0b013e328352f6fb
33. Matz EL, Hsieh MH (2017) Review of advances in uroprotective agents for cyclophosphamide- and ifosfamide-induced hemorrhagic cystitis. Urology 100:16–19. https://doi.org/10.1016/j.urology.2016.07.030
34. Morarji K, McArdle O, Hui K, Gingras-Hill G, Ahmed S, Greenblatt EM, Warner E, Sridhar S, Ali AMF, Azad A, Hodgson DC (2017) Ovarian function after chemotherapy in young breast cancer survivors. Curr Oncol 24(6):e494–e502. https://doi.org/10.3747/co.24.3335
35. Kaminska M, Ciszewski T, Kukielka-Budny B, Kubiatowski T, Baczewska B, Makara-Studzinska M, Staroslawska E, Bojar I (2015) Life quality of women with breast cancer after mastectomy or breast conserving therapy treated with adjuvant chemotherapy. Ann Agric Environ Med 22(4):724–730. https://doi.org/10.5604/12321966.1185784