Systematic Review and Meta-Analysis

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Anthracycline versus nonanthracycline adjuvant therapy for early breast cancer

A systematic review and meta-analysis

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Abstract

Purpose: The clinical benefits provided by using anthracycline-contained regimens in patients with early breast cancer (EBC) remain uncertain. This meta-analysis used data from all relevant trials to compare treatment outcomes for patients with EBC receiving adjuvant chemotherapy with non–anthracycline-contained regimens or anthracycline-contained regimens.

Patients and Methods: Individual patient data were collected on 7 randomized trials comparing non–anthracycline-contained regimens with anthracycline-contained regimens, a total of 14,451 women were analyzed. The hazard ratios (HR) of disease-free survival (DFS) and overall survival (OS), and the risk ratios for grades 3 to 4 toxicities were extracted from the retrieved studies and analyzed using various statistical methods. A pooled analysis was accomplished and HR with 95% confidence intervals (95% CIs) was derived. The significant differences in DFS and OS were explored. A heterogeneity test was applied as well.

Results: Among 7 eligible trials, significant differences in favor of anthracycline-contained regimens were seen in DFS (HR: 0.86; 95% CI: 0.78–0.95; $P = .003$) and in OS (HR: 0.85; 95% CI: 0.75–0.97; $P = .01$). Subgroup analyses of DFS showed similar treatment effects by hormone-receptor status and nodal status, but differential effects by human epidermal growth factor receptor 2 status, menopausal status, and malignancy grade. Sensitive analysis showed that the DFS of taxanes and cyclophosphamide (TC) was noninferior to anthracycline-contained regiments.

Conclusion: Despite failing to show noninferior to the anthracycline-contained regimens in patients with EBC, it provides evidence that both regimens significantly improved the DFS and OS, and TC regimen may be noninferior to anthracycline-contained regimens.

Abbreviations: AC = doxorubicin and cyclophosphamide, ASCO = American Society of Clinical Oncology, CI = confidence intervals, CMF = cyclophosphamide, methotrexate, and 5-fluorouracil, DFS = disease-free survival, EBC = early breast cancer, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, non-A = non–anthracycline-contained regimens, OS = overall survival, RCT = randomized controlled trial, RR = risk ratio, TC = taxanes and cyclophosphamide, TCH = docetaxel, carboplatin, and trastuzumab, *TOP2A* = topoisomerase II a.

Keywords: adjuvant chemotherapy, anthracycline, disease-free survival, early breast cancer, overall survival, toxic

1. Introduction

Breast cancer is the second leading cause of cancer-related deaths in women in the Western world. The administration of adjuvant chemotherapy reduces the likelihood of recurrence and improves the survival in patients with early breast cancer (EBC).[1] EBC is defined as the cancer does not spread out of the breast or the axillary lymph nodes. Treatment with adjuvant chemotherapy is recommended for women with resected node-positive or high-risk node-negative breast cancer, and an anthracycline-contained regimen is often included.[2] The use of anthracycline-containing regimens provides superior treatment benefits, when compared with CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) combination,[3] whereas the incorporation of taxanes further improved patient outcome in the adjuvant setting.[4] Anthracyclines have been the backbone of adjuvant chemotherapy for breast cancer in the last 30 years. However, anthracycline-contained regimens are associated with the risk of long-term cardiotoxicity,[5,6] which could be potentiated by the use of human epidermal growth factor receptor 2 (HER2)-targeted therapies.[7,8] More recently, non–anthracycline-contained regimens (non-A) are actively sought to spare patients with EBC from the long-term consequences of cardiotoxicities.[9,10]

Although some recent clinical trials have shown that non-A may be noninferior to anthracycline-contained regimens in the adjuvant setting, other trials have yielded the opposite result. A quantitative analysis, such as a meta-analysis, would be beneficial to investigators because it can help define the benefits and risks of using anthracycline-contained regimens or non-As for patients with EBC.

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WD, ZL, and CW contributed equally to this work.

Availability of data and materials: All data and materials used in this research are freely available in PubMed, Embase, and Cochrane Library. References have been provided.

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Here, we conducted a meta-analysis of randomized controlled trials (RCTs) to determine whether using non-A is noninferior to using anthracycline-contained regimens in treatment of EBC.

2. Patients and methods

2.1. Trials identification

Trials were eligible if they were randomized, presented before April 2018, and compared anthracycline contained regimens versus non-A for the treatment of patients with EBC.

PubMed, Embase, and Cochrane Library were used to identify all eligible trials. Keywords used were "early breast cancer," "adjuvant chemotherapy," "docetaxel or paclitaxel," "doxorubicin or epirubicin." Furthermore, we searched abstracts and presentations reported from annual meetings of the American Society of Clinical Oncology (ASCO), or the San Antonio Breast Cancer Symposium to collect relevant unpublished studies. Lastly, all review articles and all crossreferenced manuscripts from retrieved articles were screened for relevant studies. No language restriction was applied.

2.2. Selection criteria

To perform the meta-analysis, retrieved studies had to meet the following inclusion criteria: patients with EBC that had not spread out of the breast or the axillary lymph nodes; previously untreated patients who had undergone curative surgical resection and were subsequently randomized to receive either non–anthracycline-contained or anthracycline-contained regimens; and patients with standard postoperative radiotherapy and adjuvant hormonal treatment, in which tamoxifen or aromatase inhibitors were allowed, whereas trastuzumab or other targeted drugs were not allowed.

2.3. Outcomes for analysis

The primary outcome for the magnitude of eventual benefit analysis was the disease-free survival (DFS), defined as the time between randomization and appearance of recurrence (local or distant or both) or death from any cause. The secondary end point was overall survival (OS), defined as the time between randomization and death for any cause. Regarding to toxicity, we considered both hematologic (neutropenia, febrile neutropenia) and nonhematologic (vomiting, diarrhea, fatigue, stomatitis, sensory neuropathy, and cardiac dysfunction) grade 3 and 4 side effects of treatments.

2.4. Data extraction

The following information was extracted from each trial: study design, year of reporting, regimen details, number of patients assigned, median follow-up, hazard ratios (HRs) for the analyzed arms, number of outcome events, and percentage of patients who experienced grades 3 and 4 toxicity. All data were reviewed and respectively computed by 2 different independent investigators who were blinded to each other's results, using a standardized data recording form. When there was a discrepancy on an outcome, a third investigator reviewed the data and the consensus was reached at the end.

2.5. Risk of bias assessment

Review Manager 5.3 from the Cochrane Collaboration was used to assess the risk of bias in individual studies. Uniform criteria were recommended by the Cochrane Collaboration, which included 6 items: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential bias as previously used were applied in our meta-analysis.

2.6. Quantitative data synthesis

A meta-analysis was performed to evaluate the overall efficacy of treatments (nonA vs A) based on prespecified endpoints. Regarding to the primary and secondary endpoints, survival data were extracted as HR of OS and DFS with the associated confidence intervals (95% CIs). The overall efficacies of treatments in terms of adverse events were calculated by using the method employed for dichotomous data [assessment risk ratio (RR); 95% CI]. Subgroup analyses were performed to detect the influence of stratification factors and other baseline characteristics. Sensitivity analysis was used to detect the stability of the consolidated results except the trails which did not receive standard chemotherapy regimens. Statistical heterogeneity was estimated by the I^2 statistic as follows: $I^2 < 30\%$ meant "low heterogeneity"; I^2 between 30% and 50% denoted "moderate heterogeneity"; $I^2 > 50\%$ represented "substantial heterogeneity." Dichotomous outcomes were analyzed as HR (95% CI) by using the Mantel-Haenszel test. A fixed effect model was used if the heterogeneity was low or moderate. Otherwise, the random effect model was reported after exploring the cause of heterogeneity. All tests mentioned below were 2-tailed and a P value of $<.05$ was considered to be statistically significant for all analyses.

3. Results

According to the search strategy established by us, 1095 records were retrieved totally from PubMed, Embase, and Cochrane Library. After removing the duplicates and irrelevant records, 24 full-text articles were available for the meta-analysis. However, 17 records were excluded due to the following reasons: irrelevant outcome, neoadjuvant chemotherapy, study protocols of RCTs, and systemic reviews. Ultimately, 7 RCT records containing 14,451 patients were included in qualitative synthesis (Fig. 1).[11,17] The main characteristics of these included studies are listed in Table 1.

3.1. Meta-analysis of the primary outcome

The definitions of DFS between studies in this meta-analysis were quite similar. For the primary outcome DFS, there was no evidence of significant between-study heterogeneity ($P = .38$, $I^2 = 6\%$), indicating that the trials were similar enough to be combined. DFS data were available from all trials and pooled results were statistically significant in favor of anthracycline contained regimens compared with non-A ($P = .003$). The HR of 0.86 (95% CI, 0.78–0.95) represented an overall 14% lower relative risk for disease progression or death from any cause with the administration of anthracycline-contained regimens in EBC. The forest plot for DFS is shown in Figure 2.

3.2. Meta-analysis of the secondary outcome

Figure 3 shows the OS HR in individual trials and the overall. The fixed effect model was used because there was no heterogeneity ($I^2 = 0\%$, $P = .71$) between these data. The combined results favored the anthracycline-contained regimen over the non-A ($P = .01$). The HR of 0.85 (95% CI, 0.75–0.97) indicated that the

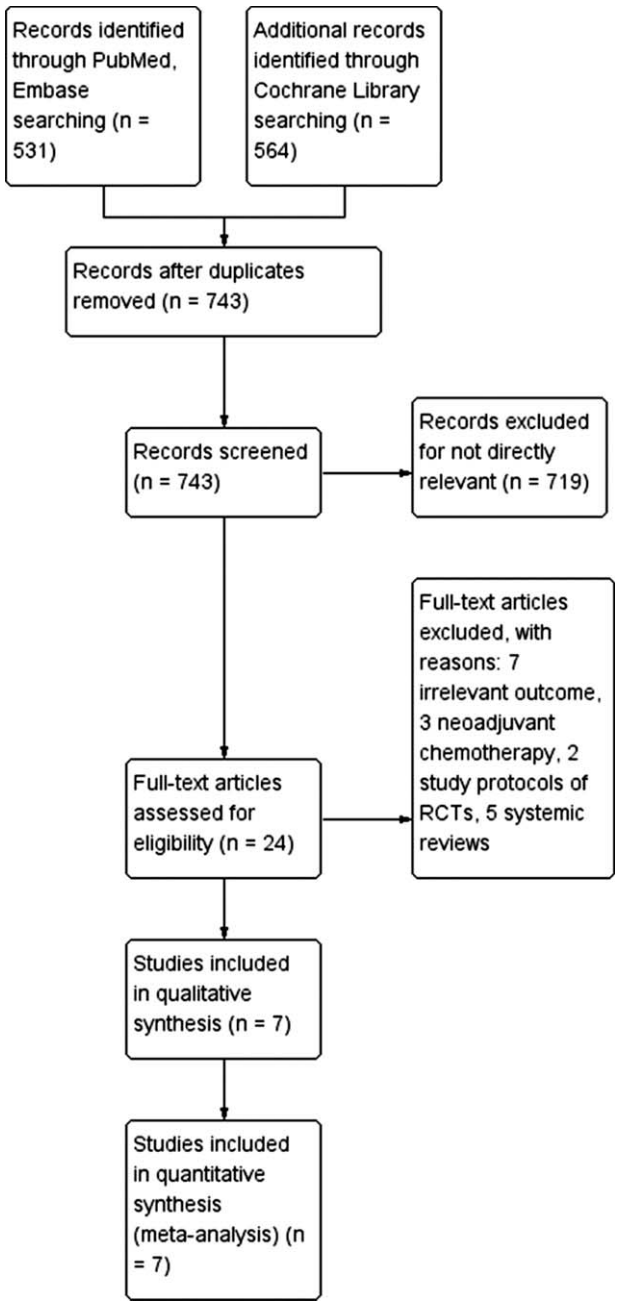

Figure 1. The flowchart of data search, collection, and selection. RCT = RCT = randomized controlled trial.

anthracycline-contained regimens in the adjuvant treatment provided a significant 15% reduction in mortality compared to the non-A in EBC.

3.3. Subgroup analysis and sensitive analysis

Subgroup analyses of DFS showed similar treatment effects by hormone-receptor status and nodal status, but differential effects by HER2 status, menopausal status, and malignancy grade. In both negative and positive HER2 groups, patients who received non-A were favored over anthracycline-contained regimens regardless of HER2 status. Premenopausal patients had better DFS after receiving non-A, and postmenopausal patients had better DFS after receiving anthracycline-contained regimens. Patients who received non-A were associated with a significant benefit in patients with grade 3 tumors, whereas in patients with grade 1 to 2 tumors, anthracycline-contained regimens were associated with improved DFS.

Sensitive analysis was performed by excepting trails of Minckwitz (2015) and Shulman (2014), whose regimens were not considered as a standard approach for the adjuvant treatment of EBC. The HR of 0.89 (95% CI, 0.79–1.00) represented that non-A (taxanes and cyclophosphamide, TC) had an overall 11% higher relative risk for disease progression or death from any cause than the anthracycline-contained regimens in EBC (Table 2).

3.4. Toxicity

Both hematologic and nonhematologic grades 3 and 4 adverse events of treatments were described in those studies. As expected, the predominant toxicity was hematologic with each regimen. Neutropenia and febrile neutropenia were much higher in anthracycline-contained regimens. Classic treatment side effects such as vomiting, diarrhea, fatigue, stomatitis, mucositis, and sensory neuropathy were common in both regimens, although vomiting was more common in anthracycline-contained regimens (Table 3). In the seven trials, the incidence of cardiac dysfunction was relatively low in both regimens. It was 0.1% in both regimens in those trails, so we did not analyze the cardiac toxicity.

3.5. Risk of bias in included RCT studies

Full details about the risk of bias of RCT studies are shown in Figure 4. For allocation concealment, the risk of bias was unclear in 2 RCTs with an allocation scheme which was not mentioned in the trials; and in the other 5 studies, the risk of bias was high. For random sequence generation, the risk of bias was unclear in 3 RCT studies and high in another one. For the attrition bias, the risk was high in 1 study.

4. Discussion

Anthracycline-contained regimens have already been an important treatment component for patients with breast cancer. As demonstrated in the last Early Breast Cancer Trialists' Collaborative Group meta-analysis, anthracycline-contained regimens decrease breast cancer mortality by 20% to 30%.[1] Anthracycline toxicities include the rare—but potentially morbid—cardiotoxicity or leukemogenic effect. Because of the potential toxicities, several worldwide trials re-examined the role of anthracycline-contained regimens in the management of breast cancer, and the updated results showed that anthracyclines were not required for all patients with breast cancer and should be avoided in those with high cardiac risk. To further assess the role of anthracycline in EBC, we performed a pooled analysis based on published articles and unpublished data. Both formal articles and abstracts were included, based on literature searches, allowing results to be gathered from all studies that meet the inclusion criteria to minimize publication bias.

HER2 amplification or overexpression might predict breast cancer responsiveness to anthracyclines in the adjuvant setting, which had been proven in National Surgical Adjuvant Breast and Bowel Project trials B11 and MA.5.[18,19] However, the BCIRG-006 trial compared an adjuvant nonanthracycline regimen of docetaxel, carboplatin, and trastuzumab (TCH) with a sequential anthracycline-containing regimen of doxorubicin, cyclophosphamide, and docetaxel with and without trastuzumab, in patients

Table 1

Characteristics of included studies and outcome events.

Trials	Jones 2009[11]	Shulman 2014[12]	Minckwitz 2015[13]	Mavroudis 2016[14]	Ejlertsen 2017[15]	Goetz 2017[16]	Harbeck 2017[17]
Information of the included trials							
Trials	USOR 9735	CALGB 40101	ICE II-GBG 52	HORG	DBCG 07-READ	USOR 06–090, NSABP B-46-I/USOR 07132, NSABP B-49	WSG PlanB
Phases	III	III	II	III	III	III	III
Accrual dates	Between July 1, 1997, and January 5, 2000	Between 2002 and 2010	Between April 2009 and April 2013	Between October 2007 and December 2013	Between June 2008 and December 2012	Between May 29, 2007 and November 21, 2013	Between 2009 and 2011
Patient characteristics and study designs							
Inclusion criteria	Age 18 to 75 years; operable stage I-III invasive breast cancer	Age ≥18 years; operable breast cancer; pN0 ER+ T≥1cm; ER-; pN+;	Age ≥65 years; CCI≤2; cM0; pT1/2 pN0/1 high-risk; pT3/4 pN2/3;	Age 18 to 75 years; free margins; N+; HER2-	pN0 high-risk; pN+; TOP2A-Normal operable breast cancer;	pN0 high-risk; pN+; free margins; pT1-3; cM0;	Age ≤75 years; HER2-; cM0; free margins; pN0 high-risk; pN+
Study designs	AC 60/600 * 4 TC 75/600 * 4	AC 60/600 * 4 or 6 P 175 * 4 or 6	EC 90/600 * 4/CMF 500/40/600 * 6 nPX 100/2000 * 6	FEC 75/50/500 * 4 → T 75 * 4 TC 75/600 * 6	EC 90/600 *3→T 100 * 3 TC 75/600 * 6	TAC 75/50/500 * 6 TC 75/600 * 6	EC 90/600 * 4→T 100 * 4 TC 75/600 * 6
Medium follow-up, mo	84	73.2	22.8	46	69	39.6	60
No. patients	AC: 510 TC: 506	AT: 1931 P: 1940	EC/CMF: 185 nPX: 124	FEC→T: 326 TC: 324	EC→T: 994 TC: 1006	TAC: 2062 TC: 2094	EC→T: 1227 TC: 1222
Outcomes assessment							
Primary end point	Disease-free survival; overall survival	Disease-free survival	Safety	3-Year disease-free survival rate	Disease-free survival	Invasive disease-free survival	Disease-free survival
Secondary end point	Disease-free survival (age, HER2 status, and hormone receptor status)	Overall survival	Invasive disease-free survival and overall survival	Overall survival	Overall survival;	Overall survival and safety	Overall survival and safety

+ = positive, − = negative, AC = doxorubicin and cyclophosphamide, AT = doxorubicin and doxorubicin, CALGB = Cancer and Leukemia Group B, CCI = Charlson Comorbidity Index, CMF = cyclophosphamide, methotrexate, and 5-fluorouracil, DBCG = Danish Breast Cancer Cooperative Group, EC = epirubicin and cyclophosphamide, ER = estrogen receptor, FEC = 5-fluorouracil, epirubicin, and cyclophosphamide, HER2 = human epidermal growth factor receptor 2, HORG = Hellenic Oncology Research Group, ICE II-GBG = Investigational Chemotherapy for Elderly patients II —German Breast Group, nPX = Nab-paclitaxel and capecitabine, NSABP = National Surgical Adjuvant Breast and Bowel Project, P = paclitaxel, TAC = docetaxel, doxorubicin, and cyclophosphamide, TC = docetaxel and cyclophosphamide, TOP2A = topoisomerase II a, USOR = United States Oncology Research, WSG = West German Study Group.

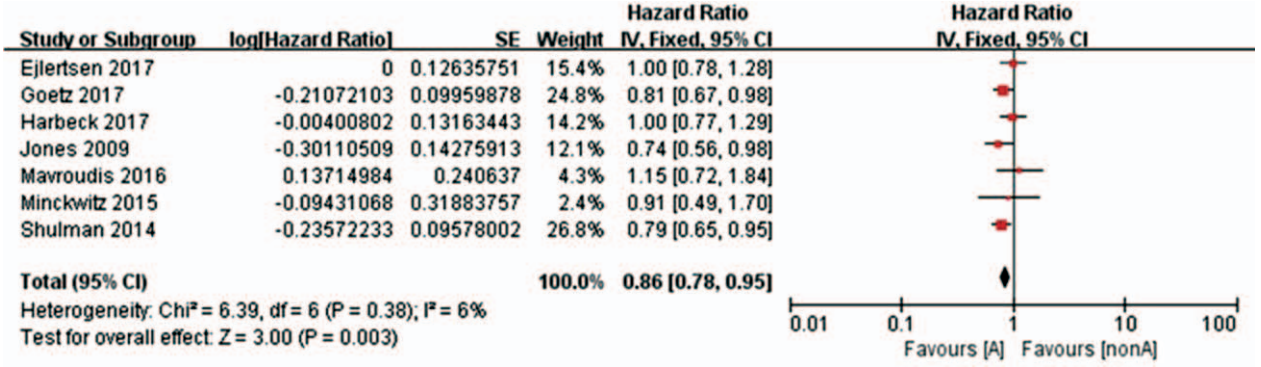

Figure 2. Forest plot of comparison: disease-free survival. CI = confidence interval.

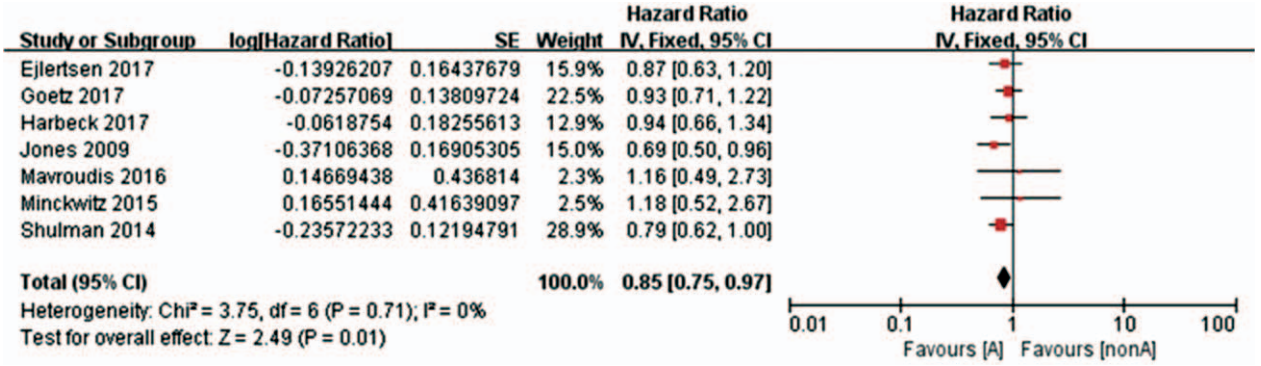

Figure 3. Forest plot of comparison: overall survival. CI = confidence interval.

Table 2

Subgroup analysis and sensitivity analysis for disease-free survival.

	HR (95% CI)	*P*	I^2%
1. Subgroup analysis			
Hormone-receptor status			
ER and PR (–)	0.98 (0.71, 1.35)	.09	55
ER and/or PR (+)	1.02 (0.86, 1.21)	.43	0
HER2 status			
HER2 –	1.01 (0.82,1.26)	.19	35
HER2 +	1.37 (0.59,3.16)	.46	–
Malignancy grade			
Grade ½	0.73 (0.53,1.00)	.29	20
Grade 3	1.36 (1.01,1.85)	.59	0
Nodal status			
0	0.97 (0.69, 1.36)	.86	–
1–3	0.95 (0.58, 1.54)	.16	50
4–10	0.80 (0.52,1.21)	.40	0
>10	0.80 (0.46,1.40)	.06	72
Menopausal status			
Postmenopausal	0.87 (0.63,1.20)	.29	10
Premenopausal	1.29 (0.92,1.79)	.88	0
2. Sensitivity analysis			
A vs TC	0.89 (0.79,1.00)	.26	24

+ = positive, – = negative, A = anthracycline contained regimen, CI = confidence interval, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, PR = progesterone receptor, TC = docetaxel and cyclophosphamide.

with HER2-positive EBC. The trial showed the results that no significant differences in efficacy (DFS or OS) were found between the 2 trastuzumab regimens (AC-TH vs TCH). The DFS benefit was independent of nodal status and tumor size of patient. This trail also showed that the non-A (TCH) was thus an acceptable adjuvant chemotherapy regimen in patients with HER2-positive EBC.[10]

In fact, other studies suggested that the reason for increasing efficacy of anthracyclines in HER2 amplification patients might be related to the proximity of the *HER2* gene and the topoisomerase II a (*TOP2A*) gene.[20]*TOP2A* is an essential enzyme resolving topologic DNA constraints, which locates on chromosome 17 q21–22 and was found to be amplified in 35% of HER2-positive BC.[21–23] A pooled analysis of Danish Breast Cancer Cooperative Group 89D trial together with four additional phase III trials confirmed a greater benefit from

Table 3

Grade 3 to 4 toxicity.

Outcome	RCTs	RR	95% CI	*P*	I^2, %
Neutropenia	6	1.65	0.87–3.13	.13	97
Febrile neutropenia	7	1.20	0.65–2.21	.56	75
Vomiting	7	4.29	2.37–7.75	<.00001	21
Diarrhea	7	0.71	0.40–1.25	.24	62
Fatigue	7	1.31	0.90–1.91	.15	56
Mucositis	6	1.91	0.98–3.74	.06	40
Sensory neuropathy	6	0.97	0.36–2.61	.95	79

CI = confidence interval, RCT = randomized controlled trial, RR = risk ratio.

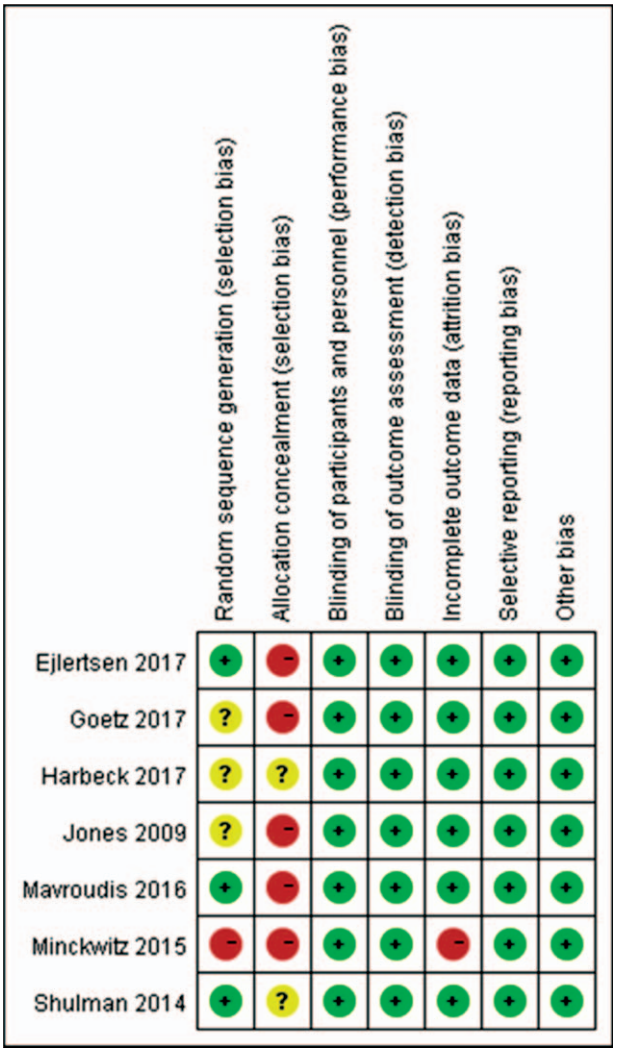

Figure 4. Risk of bias: a summary table for each risk of bias item for each study.

anthracyclines in patients with *TOP2A* alterations and a trend toward greater benefit in patients with *HER2*-amplified tumors, which provided that the benefit of anthracyclines was largely confined to the subgroup of patients with *TOP2A*-altered tumors.[24]

Chromosome 17 centromeric duplication (Ch17CEP) has also been evaluated as a potential predictive biomarker for anthracycline sensitivity.[25] In a pooled analysis of 5 trials that compared anthracycline-contained chemotherapy with CMF, both *CEP17* and *TOP2A* treatment-by-marker interactions remained significant in adjusted analyses for DFS and OS, whereas *HER2* did not. A combined *CEP17*- and *TOP2A*-adjusted model predicted anthracycline benefit across all 5 trials for both DFS (HR = 0.64; $P = .001$) and OS (HR = 0.66; $P = .005$).[26] These data suggested that HER2 might not be a predictor of benefit from anthracyclines, and *CEP17* and *TOP2A* alterations seem like potential biomarkers of anthracycline benefit regardless of *HER2* status.

Given that *HER2* expressing tumors might increase sensitivity to anthracyclines, it had been argued that the inclusion of such patients might lead to an overestimation of the benefit derived from anthracyclines. The ABC Trials, which only included patients of *HER2*-normal breast cancer, showed that patients with *HER2*-normal derived some benefits from anthracyclines that could owe to the joint analysis, which was unable to demonstrate noninferiority of adjuvant taxanes and cyclophosphamide (TC) compared with doxorubicin and cyclophosphamide followed by paclitaxel.[16] And our meta-analysis demonstrated a statistically significant improvement in DFS with the administration of anthracyclines in patients with EBC. Subgroup analyses by stratification variables suggested that the benefit of anthracycline-contained regimens was more evident for the patients who had the highest number of positive axillary lymph nodes. Those results suggested that anthracyclines should not be spared in patients with high risk of breast cancer recurrence such as those with triple negative disease or *HER2*−/hormone positive with significant axillary node involvement.

Despite those treatments proven efficacy, there was one growing concern regarding the long-term toxicity of anthracycline-contained chemotherapy. Anthracyclines had been linked to an increased risk of cardiomyopathy and heart failure, especially in combination use with new drugs that target the *HER2*.[27,28] This risk might be further exacerbated by the administration of adjuvant radiotherapy in women with left-sided tumors.[29] Although dexrazoxane was approved for use to prevent anthracycline-related toxicity, there was a concern that it might lead to the decreased antitumor efficacy,[30] and ASCO recommended against routine use of prophylactic dexrazoxane in the adjuvant setting.[31] This meta-analysis failed to show noninferiority for the non-A, but the absolute benefits were small, and sensitivity analysis results showed the majority of patients who received TC had done well without an anthracycline. In addition, toxicity including both hematologic and nonhematologic grade 3 and 4 side effects of treatment differed among all trials, anthracycline-contained regimens had relatively high incidence of neutropenia and febrile neutropenia compared with non-A (21% vs 17%, RR = 1.65, $P = .13$; and 2.9% vs 2.4%, RR = 1.20, $P = .56$). Therefore, the role of anthracyclines should come under close scrutiny, especially for patients with low or intermediate risk for disease recurrence.

The meta-analysis we performed had certain limitations should be discussed. First, a possible limitation of this meta-analysis was that it used information obtained from published data rather than individual patient information. However, our meta-analysis included clinical trials conducted with patients having EBC, and they were thus highly comparable in terms of their prognosis. Second, the number of studies included was relatively small and affected the power of the meta-analysis to reveal statistically significant results. Nonetheless, we had systematically identified all the available randomized studies, either published in peer-reviewed journals or presented in major international cancer congresses, so as to our analysis, all the available randomized trials on this topic were included.

5. Conclusion

Despite failing to show noninferior to the non-A in patients with EBC, it provided evidence that both regimens significantly improved the DFS and OS, and TC regimen may be noninferior to anthracycline-contained regimens.

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Author contributions

CT designed the study and developed the analysis plan. WD and ZL analyzed the data and performed meta-analysis. CW and WD assessed the risk of bias. WD contributed in writing of the article. JD and GR revised the manuscript and polished the language.
Conceptualization: Wu Ding.
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Methodology: Wu Ding, Zhian Li.
Project administration: Wu Ding.
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Validation: Jiangfeng Dai.
Visualization: GuoDong Ruan, Jiangfeng Dai.
Writing - original draft: Wu Ding.
Writing - review and editing: Chuanjian Tu.

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