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Role of Taxane and Anthracycline Combination Regimens in the Management of Advanced Breast Cancer

A Meta-Analysis of Randomized Trials

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Abstract: The clinical benefits provided by using combined taxanes and anthracyclines in first-line chemotherapy for metastatic breast carcinoma (MBC) remain uncertain. This meta-analysis compares the benefits of using a combination of anthracyclines along with taxanes versus using single-agent-based chemotherapeutic regimens in the treatment of MBC.

Relevant clinical trials as well as abstracts from articles presented at major cancer conferences were searched in various databases including PubMed, Embase, and Cochrane Library. The relevant studies had a primary endpoint of overall survival (OS) and secondary endpoints that included progression-free survival (PFS), time-to-treatment failure (TTF), time to progression (TTP), objective response rate (ORR), disease control rate (DCR), and safety. The hazard ratios of OS, PFS, TTF, and TTP, the odds ratios of ORR and DCR, and the risk ratios (RRs) for grades 1–2 and 3–4 toxicities were extracted from the retrieved studies and analyzed using various statistical methods. Meta-analytic estimates were derived from a random-effect model.

Fifteen trials were included in the final meta-analysis, and the results suggest that chemotherapy with combined anthracyclines and taxanes does not significantly improve the OS of MBC patients when compared with the OS achieved using separate taxane or anthracycline-based regimens. Compared with taxane-based regimens, combined taxane along with anthracycline regimens failed to significantly improve TTP, ORR, or DCR, but did significantly improve TTP and ORR when compared with anthracycline-based regimens. Furthermore, both individual taxane-based and anthracycline-based regimens produced fewer toxic reactions compared to combined taxane along with anthracycline regimens. Taxane-based regimens had lower RRs for side effects of neutropenia, infection/febrile neutropenia, nausea, and vomiting, whereas patients receiving anthracycline-based regimens had lower RRs for neutropenia, infection/febrile neutropenia, anorexia, stomatitis/mucosal inflammation, diarrhea, and sensory neuropathy. In contrast, patients receiving taxane-based regimens were at higher RRs for hand–foot syndrome and diarrhea, whereas patients receiving anthracycline-based regimens had higher RRs for nausea and vomiting.

A taxane-based treatment regimen may be a better option than a combined taxane/anthracycline regimen for managing patients with advanced breast cancer, as it produces equivalent clinical outcomes and has less toxicity compared to other similar regimens.

(*Medicine* 94(17):e803)

Abbreviations: CI = confidence interval, DCR = disease control rate, HR = hazard ratio, MBC = metastatic breast carcinoma, ORR = objective response rate, ORs = odds ratios, OS = overall survival, PFS = progression-free survival, RCTs = randomized clinical trials, RRs = risk ratios, TTF = time-to-treatment failure, TTP = time to progression.

INTRODUCTION

Breast cancer is the second most frequent cause of cancer-related death among women in China. When treating patients with metastatic breast carcinoma (MBC), combination chemotherapy regimens yield a higher objective response rate (ORR) and a longer median time to progression (TTP) when compared with single-agent chemotherapy. Anthracyclines are frequently utilized in treatment of MBC, regardless of which other chemotherapeutic agents are administered. Furthermore, anthracycline-based combination therapies improves both the ORR and TTP when compared to treatment regimens without anthracycline.[1] In a Phase II trial, an anthracycline-based combination treatment yielded ORRs ranging from 35% to 70%.[2] Since the 1990s, taxanes have been offered as a standard treatment option for patients with MBC, and the China Food and Drug Administration has approved their use in treating patients with MBC. Several randomized clinical trials (RCTs) have shown that paclitaxel and docetaxel are 2 of the most effective agents for treating MBC. When used in first-line chemotherapy, paclitaxel and docetaxel-based therapies have yielded ORRs of 32% to 62% and 40% to 68%, respectively.[2] However, hematologic toxicity often limits the use of combined anthracycline and taxane therapy.

Although recent clinical trials have compared the efficacies of combined anthracycline along with taxane (A-T) regimens with those of anthracycline-based (A-nonT) and taxane-based (T-nonA) regimens, the exact benefits realized by using a

Editor: Giovanni Corso.
Received: January 19, 2015; revised: March 25, 2015; accepted: April 1, 2015.
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No funding source had any role in the design of this study, the collection, analysis, and interpretation of data, or the writing of this manuscript. All authors had access to the raw data. The corresponding author had full access to all of the data, and made the final decision on whether to submit the manuscript for publication.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000803

combination of such drugs remains largely uncertain because of the small numbers of patients studied. A quantitative analysis, such as a meta-analysis, is beneficial to investigators because it can help define the benefits and risks of using combined taxane along with anthracycline regimens as first-line chemotherapy for patients with MBC.[3,4]

In current evidence-based medicine, large RCTs or meta-analyses of past studies are often used to obtain advice when selecting methods for treating disease. This is especially true when the existing RCTs include only small numbers of patients, fail to reach their specified endpoints, or provide conflicting results.[5,6] We conducted this meta-analysis of RCTs and presentations at major meetings to determine whether using a combination of anthracyclines and taxanes is superior to using anthracyclines or taxanes by themselves in treatment of MBC. Our primary outcomes were comparisons of overall survival (OS) rates achieved using A-T versus A-nonT as well as A-T versus T-nonA chemotherapy regimens. Our secondary outcomes included TTP, progression-free survival (PFS), time-to-treatment failure (TTF), ORR, disease control rate (DCR), and major toxicities.

METHODS

Searches

Widely recognized large databases (PubMed, Embase, and the Central Registry of Controlled Trials of the Cochrane Library) were searched for meeting (ASCO and ESMO) abstracts, and results of selected studies presented between January 1990 (the time when taxane treatment was first introduced for patients) and January 2014. Only prospective studies were selected to minimize the risk of selection or information bias.[7–9] The search was performed by using the following keywords and their various combinations: "breast," "tumor," "cancer," "advanced," "metastatic," "chemotherapy," "taxanes," "anthracyclines," "prospective," and "randomized." Epirubicin and doxorubicin are 2 major anthracyclines, and epirubicin or doxorubicin was also used as a keyword for searching relevant studies. All relevant studies and their reference lists were examined, and there was no limitation regarding the language of the publication.

Selection

All studies included in our meta-analysis were required to satisfy the following criteria:

1. The study reported a diagnosis of advanced breast cancer or metastatic disease, as well as demographic characteristics of the study population (age, sex, and performance status).
2. Taxanes or anthracyclines were used either alone or in combination as first-line therapy in cases of advanced-stage breast cancer.
3. The included patients had no major comorbidities or secondary tumors (except for nonmelanoma skin cancers or localized cervical tumors).
4. Patients in the control arm received either an anthracycline or taxane-based treatment regimen, whereas patients in the experimental arm were treated with a combination of taxanes and anthracyclines.
5. Tumor staging and subsequent follow-up results were reported.

Exclusion Criteria

The following types of studies were excluded from our meta-analysis: noncomparative studies and nonprospective studies; studies in which taxanes and (or) anthracyclines were used as other than first-line therapies; studies with noncomparable endpoints; and studies in which the chemotherapeutic agents were given by a nonsystemic or oral route of administration (eg, intraarterial or intraperitoneal infusion).

Data Extraction

The selected studies were independently examined by 2 investigators (R.Z. and S.W.) to screen for homogeneity.[10] Different variables from the selected trials (eg, number of patients enrolled, year of publication, treatment schedule, and clinical efficacy) were extracted and evaluated. Data regarding the incidence of toxicities were obtained from the safety profile of each study. Disagreements regarding study selection were resolved by an arbiter (P.T.). The primary endpoint was OS, and secondary endpoints were PFS, TTF, TTP, ORR, DCR, and safety.

Validity Assessment

Selected studies were evaluated for their quality based on the following 4 factors described in the *Cochrane Reviewers' Handbook*: method of randomization, allocation concealment, blindness, and adequacy of follow-up.[11,12] Six trials received a score of A (low risk of bias), 5 received a score of B (intermediate risk of bias), and 4 were scored as C (high risk of bias).

Quantitative Data Synthesis

A meta-analysis was performed to evaluate the overall efficacy of combination treatments (taxanes in combination with anthracyclines) based on prespecified endpoints.[13] Regarding the primary and secondary endpoints, survival data was extracted as hazard ratios (HRs) of OS, PFS, TTF, and TTP with the associated confidence intervals (95% CIs). The overall efficacies of combined treatments in terms of ORR, DCR, and adverse events were calculated using the method employed for dichotomous data (assessment odds ratio [OR] and risk ratio [RR]; 95% CI). A subgroup analysis based on the class of chemotherapeutic agents was performed for all endpoints. Cochrane Q test and I^2 statistics were used to assess heterogeneity between studies, and the random-effects model was used to perform an analysis that compared data from clinical trials that utilized drugs with different mechanisms of action.[14] A pooled data analysis was performed according to procedures used for the DerSimonian and Laird test.[15,16] The possibility of publication bias was investigated using Begg test and by visual inspections of funnel plots.[17] All statistical analyses were performed using the R version 3.1.0—a language and environment for statistical computing.[18] A 2-tailed P value <0.05 was considered statistically significant.

RESULTS

Study Characteristics

During time span covered by this review, 406 prospective clinical studies on breast cancer were reported as full articles or meeting abstracts. We screened 44 RCTs conducted with MBC patients who were allocated to receive therapy with combined taxanes and anthracyclines and then compared with patients allocated to receive treatment with either an anthracycline or taxane-based combination regimen.[19–34] Fifteen trials including a total of 3623 patients were finally selected for inclusion in the final meta-analysis (Figure 1). Each selected trial had at

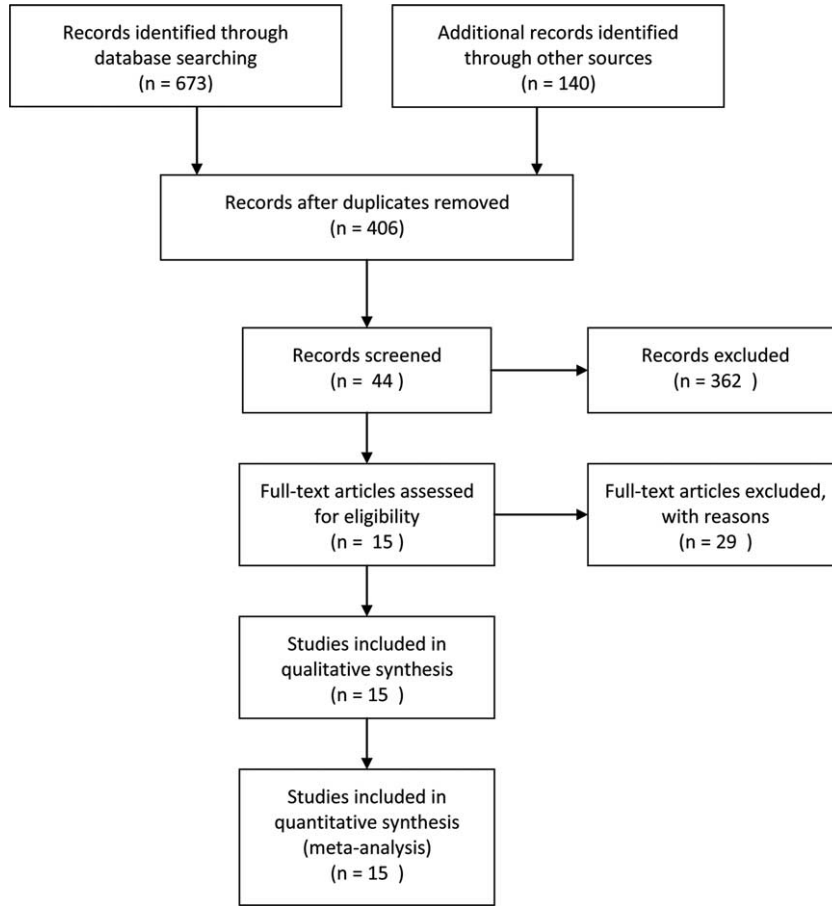

FIGURE 1. Flow diagram showing exclusion and inclusion of trials in this meta-analysis.

least 1 index (OS, PFS, TTF, TTP, ORR, or DCR) that made it eligible for our endpoint analysis (Table 1).

Taxane-based combination regimens were evaluated in 6 RCTs involving 949 patients (taxanes combined with capecitabine in 4 RCTs involving 807 patients and taxanes combined with platinum in 2 RCTs involving 415 patients).[20–25]

Anthracycline-based combination regimens were evaluated in 12 RCTs involving 2401 patients (anthracyclines combined with cyclophosphamide in 6 RCTs involving 1776 patients and anthracyclines along with 5-fluorouracil and cyclophosphamide in 3 RCTs involving 625 patients). Gebbia et al[30] had conducted a clinical trial that randomly assigned the patients to 3 arms; however, only the paclitaxel along with epidoxorubicin and cyclophosphamide in combination with epidoxorubicin arms were selected for inclusion in our meta-analysis.[25–34]

Quantitative Data

Among the 15 eligible RCTs, 12 trials reported data related to OS in terms of HR, and these data were included in the OS analysis. Unfavorable evidence from combined taxane along with anthracycline regimens compared with anthracycline or taxane-based combination regimens originated from the HR analysis in terms of OS (HR: 1.004; 95% CI: 0.844–1.196 and HR: 0.937; 95% CI: 0.788–1.115; Figure 2). A subgroup analysis identified a nonstatistically significant advantage regarding OS for both taxane along with capecitabine therapy (HR: 0.980; 95% CI: 0.784–1.225), and taxane along with platinum therapy (HR: 1.044; 95% CI: 0.790–1.380), whereas the combination of anthracyclines and cyclophosphamide failed to show a significant advantage (HR: 1.042; 95% CI: 0.932–1.166). However, the subgroup combination of anthracyclines, 5-fluorouracil, and cyclophosphamide revealed a survival trend favoring combination therapy with taxanes and anthracyclines (HR: 0.696; 95% CI: 0.576–0.841).

Four of the 15 RCTs included in this meta-analysis reported results of a PFS analysis. The TTF analysis in 2 eligible RCTs and TTP analysis in 6 HR analyses showed that use of combined taxanes and anthracyclines did not yield significantly higher efficacy when compared with combined taxane along with capecitabine therapy in terms of PFS and TTP (HR for PFS: 1.159, 95% CI: 0.741–1.813 and HR for TTP: 1.072; 95% CI: 0.849–1.354). Furthermore, combined taxanes and anthracyclines showed lower efficacy when compared to a combination regimen of taxanes along with platinum in terms of TTF (HR for TTF: 1.321; 95% CI: 1.050–1.663) (Table 2). However, the combined regimen of taxanes and anthracyclines showed higher efficacy when compared with a triple combination therapy consisting of anthracyclines, 5-fluorouracil, and cyclophosphamide in terms of TTP (HR for TTP: 0.703; 95% CI: 0.587–0.843). Additionally, the taxanes along with anthracyclines regimen was superior to a combined anthracyclines and cyclophosphamide regimen in terms of TTP (HR for TTP:

TABLE 1. Main Characteristics of Randomized Trials Included in This Meta-Analysis

			Treatment		ORR, %		DCR, %		PFS, m		TTF, m		TTP, m		OS, m	
Trials	**Year**	**Patients**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**
Yang et al[20]	2013	92	TA+AN	TA+CA	63	72	NA	NA	NA	NA	NA	NA	8.7	10.2	NA	NA
Luck et al[21]	2013	340	TA+AN	TA+CA	42	47	78	78	9.2	10.4	NA	NA	NA	NA	26.1	22
Bachelot and Bajard[22]	2011	68	TA+AN	TA+CA	48	64	72	72	6.8	12.4	NA	NA	NA	NA	NA	NA
Mavroudis et al[23]	2010	307	TA+AN	TA+CA	51	51	85	81	NA	NA	NA	NA	10.6	11.0	37.6	35.7
Wang et al[24]	2008	88	TA+AN	TA+PL	48	61	85	93	NA	NA	NA	NA	10.0	8.0	NA	NA
Fountzilas et al[25]	2004	327	TA+AN	TA+PL	47	42	78	81	NA	NA	8.1	10.8	NA	NA	22.4	27.8
Blohmer et al[26]	2010	240	TA+AN	AN+CY	47	42	66	63	NA	NA	NA	NA	10.3	10.1	30	19.9
Langley et al[27]	2005	705	TA+AN	AN+CY	64	54	88	87	7	7.1	NA	NA	NA	NA	13	14
Lyman et al[28]	2004	91	TA+AN	AN+CY	31	39	58	46	NA	NA	NA	NA	NA	NA	14	27
Nabholtz et al[29]	2003	429	TA+AN	AN+CY	59	47	83	79	NA	NA	6.4	5.9	9.3	8.0	22.5	21.7
Gebbia et al[30]	2003	38	TA+AN	AN+CY	65	50	90	72	NA	NA	NA	NA	NA	NA	NA	NA
Biganzoli et al[31]	2002	273	TA+AN	AN+CY	58	54	82	80	6	6	NA	NA	NA	NA	20.6	20.5
Jassem et al[32]	2009	267	TA+AN	PY+AN+CY	60	52	83	86	NA	NA	NA	NA	8.1	6.2	23	18.3
Bontenbal et al[33]	2005	216	TA+AN	PY+AN+CY	58	37	85	84	NA	NA	NA	NA	8.0	6.6	22.6	16.2
Bonneterre et al[34]	2004	142	TA+AN	PY+AN+CY	63	34	94	88	NA	NA	NA	NA	7.8	5.9	34	28

AN+CY = anthracyclines + cyclophosphamide, DCR = disease control rate, NA = not available, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PY+AN+CY = anthracyclines + 5-fluorouracil + cyclophosphamide, TA+AN = taxanes + anthracyclines, TA+CA = taxanes + capecitabine, TA+PL = taxanes + platinum, TTF = time-to-treatment failure, TTP = time to progression.

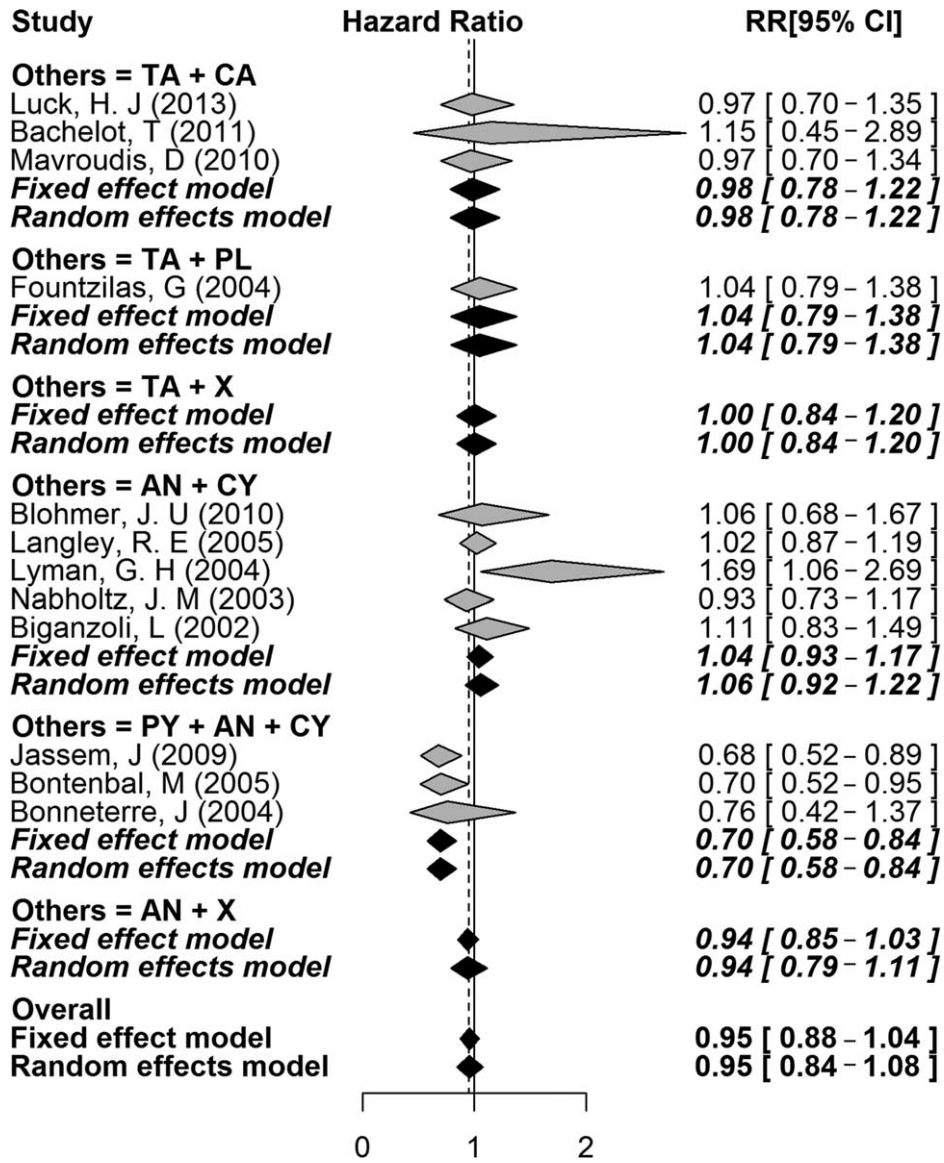

FIGURE 2. Comparison of overall survival between patients treated with combination of anthracyclines and taxanes with single agent-based regimens.

0.792; 95% CI: 0.665–0.942), but not PFS and TTF (HR for PFS: 1.034, 95% CI: 0.910–1.174 and HR for TTF: 0.835; 95% CI: 0.685–1.017) (Table 2).

Results of ORR and toxicity analyses were included in 15 RCTs, and results of DCR analyses were reported in 14 of the 15 eligible RCTs. The OR analysis revealed that combined taxanes and anthracyclines failed to show higher efficacy when compared with taxane-based therapies in terms of ORR (OR for RR: 0.907, 95% CI: 0.719–1.145) and DCR (OR for DCR: 1.530; 95% CI: 1.300–1.800). However, in a 2-armed study, combined taxanes and anthracyclines showed greater efficacy than an anthracycline-based combination therapy in terms of ORR (OR for ORR: 1.530, 95% CI: 1.300–1.800), but not DCR (OR for DCR: 1.197; 95% CI: 0.968–1.481) (Table 2).

When compared with a combined taxanes and anthracyclines group, a taxane-based combination group had significantly fewer adverse events of neutropenia (I–IV), infection/febrile neutropenia (III–IV), nausea (I–IV), and vomiting (I–IV). An anthracycline-based combination group showed lower incidences of neutropenia (III–IV), infection/febrile neutropenia (III–IV), anorexia (III–IV), stomatitis/mucosal inflammation (I–IV; III–IV), diarrhea (I–IV; III–IV), and sensory neuropathy (I–IV; III–IV). In contrast, a taxane-based combination group showed significantly higher incidences of hand–foot syndrome (I–IV) and diarrhea (III–IV) (Table 3).

A subgroup analysis revealed lower incidences of diarrhea (I–IV; III–IV), hand–foot syndrome (I–IV; III–IV), and sensory neuropathy (I–IV) in the taxanes along with capecitabine combination group, but higher incidences of leucopenia (III–IV), neutropenia (I–IV), anemia (I–IV), infection/febrile neutropenia (I–IV), nausea (I–IV), and vomiting (I–IV) in that group. The incidence of neutropenia (I–IV) in the taxanes along

TABLE 2. Comparison of ORR, DCR, PFS, TTF, or TTP Between Patients Treated With Combined Anthracyclines and Taxanes and Patients Treated With Single Agent-Based Regimens

Endpoints	Group	No. of Studies	HR	95% CI	I^2, %	*P* Values of Subgroup Differences or Total
ORR	TA+CA	4	0.831	0.623–1.108	0	<0.001
	TA+PL	2	1.071	0.722–1.588	46.5	
	AN+CY	6	1.395	1.155–1.685	0	
	PY+AN+CY	3	1.994	1.446–2.749	50	
	TA+X	6	0.907	0.719–1.145	1.1	<0.001
	AN+Y	9	1.530	1.300–1.799	13.4	
	TA/AN+X/Y	15	1.248	1.013–1.537	52.5	0.038
DCR	TA+CA	3	1.100	0.754–1.605	0	0.468
	TA+PL	2	0.803	0.483–1.335	0	
	AN+CY	6	1.247	0.980–1.587	0	
	PY+AN+CY	3	1.035	0.657–1.631	0	
	TA+X	5	0.983	0.726–1.330	0	0.295
	AN+Y	9	1.197	0.968–1.481	0	
	TA/AN+X/Y	14	1.122	0.943–1.335	0	0.196
PFS	TA+CA	2	1.159	0.741–1.813	51.4	0.630
	TA+PL	0	—	—		
	AN+CY	2	1.034	0.910–1.174	0	
	PY+AN+CY	0	—	—		
	TA+X	2	1.159	0.741–1.813	51.4	0.630
	AN+Y	2	1.034	0.910–1.174	0	
	TA/AN+X/Y	4	1.040	0.930–1.163	0	0.493
TTF	TA+CA	0	—	—	—	0.003
	TA+PL	1	1.321	1.050–1.663	—	
	AN+CY	1	0.835	0.685–1.017	—	
	PY+AN+CY	0	—	—	—	
	TA+X	1	1.321	1.050–1.663	—	0.003
	AN+Y	1	0.835	0.685–1.017	—	
	TA/AN+X/Y	2	1.046	0.667–1.641	88.7	0.844
TTP	TA+CA	1	1.072	0.849–1.354	—	0.019
	TA+PL	0	—	—	—	
	AN+CY	2	0.792	0.665–0.942	0	
	PY+AN+CY	3	0.703	0.587–0.843	0	
	TA+X	1	1.072	0.849–1.354	—	0.008
	AN+Y	5	0.748	0.659–0.848	0	
	TA/AN+X/Y	6	0.811	0.726–0.906	35.2	<0.001

AN+Y = anthracycline-based combination regimens, CI = confidence interval, DCR = disease control rate, HR = hazard ratio, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, TA+X = taxane-based combination regimens, TA/AN+X/Y = taxane-based + anthracycline-based combination regimens, TTF = time-to-treatment failure, TTP = time to progression.

with platinum combination group was also higher. The combined anthracyclines along with cyclophosphamide group had significantly higher incidences of nausea (I–IV) and vomiting (I–IV; III–IV), but lower incidences of neutropenia (III–IV), infection/febrile neutropenia (III–IV), anorexia (III–IV), stomatitis/mucosal inflammation (I–IV), diarrhea (I–IV; III–IV), and sensory neuropathy (I–IV; III–IV). The triple combination therapy group (anthracyclines, 5-fluorouracil, and cyclophosphamide) had a significantly lower incidence of infection/febrile neutropenia (III–IV) (Table 3). A Begg funnel plot showed no significant evidence of publication bias (Figure 3).

DISCUSSION

This study examined clinical 15 trials that compared the clinical efficacy of taxane and anthracycline combination regimens with those of taxane or anthracycline-based combination regimens in patients with MBC. Our analysis showed that use of a combined taxane along with anthracycline regimen rather than a taxane-based regimen did not significantly improve OS in MBC patients. Additionally, the combined taxane along with anthracycline regimens failed to significantly enhance TTP, ORR, and DCR as compared with taxane-based regimens. Furthermore, when compared with taxane-based regimens, combined anthracycline along with taxane regimens produced higher incidences of hematological and gastrointestinal toxicities, suggesting that use of taxane-based combination regimens, and especially the taxane along with capecitabine, may be a better approach for treating MBC patients.

Similar to Bria et al,[19] we found no significant increase in OS attributable to treatment with combined anthracyclines along with taxanes when compared to treatment with anthracycline-based regimens; however, significant benefits were observed in terms of TTP and ORR. Thus, the anthracycline-

TABLE 3. Adverse Events Recorded in the Meta-Analysis

		I–IV					III–IV				
Safety Endpoints	**Group**	**No. of Studies**	**HR**	**CI**	I^2	***P***	**No. of Studies**	**HR**	**CI**	I^2	***P***
Leukopenia	TA+CA	1	3.16	1.64–6.10	—	<0.001	3	3.41	1.64–7.09	53.3	
	TA+PL	0	—	—	—		0				
	AN+CY	0	—	—	—		2	1.30	0.78–2.15	0	
	PY+AN+CY	0	—	—	—	—	1	1.59	0.81–3.14	—	0.1
	TA+X	0	—	—	—		3	3.41	1.64–7.09	53.3	
	AN+Y	0	—	—	—	—	3	1.39	0.93–2.09	0	0.037
	TA/AN+X/Y	1	3.16	1.64–6.10	—	<0.001	6	2.05	1.17–3.59	69.2	0.013
Neutropenia	TA+CA	2	1.91	1.35–2.69	0		3	1.14	0.84–1.56	33.2	
	TA+PL	1	3.15	1.10–8.98	—		1	1.73	0.69–4.33	—	
	AN+CY	1	3.4	0.92–12.53	—		3	2.3	1.47–3.60	34	
	PY+AN+CY	—	—	—	—	0.500	1	1.38	0.69–2.74	29.7	0.089
	TA+X	3	2.00	1.44–2.77	0		4	1.19	0.89–1.6	19.1	
	AN+Y	1	3.40	0.92–12.53	—	0.438	4	1.98	1.37–2.88	31	0.035
	TA/AN+X/Y	4	2.07	1.51–2.84	0	<0.001	8	1.45	1.16–1.83	41	0.001
Anemia	TA+CA	3	2.38	1.61–3.50	0		4	0.86	0.33–2.2	0	
	TA+PL	1	2.13	0.7–6.47	—		1	1.44	0.06–36.38	—	
	AN+CY	0	—	—	—		1	0.62	0.19–2.01	—	
	PY+AN+CY	0	—	—	—	0.855	1	3.18	0.32–31.32	—	0.649
	TA+X	4	2.35	1.63–3.39	0		5	0.89	0.36–2.20	0	
	AN+Y	0	—	—	—	—	2	0.92	0.34–2.40	0	0.969
	TA/AN+X/Y	4	2.35	1.63–3.39	0	<0.001	7	0.91	0.46–1.77	0	0.770
Thrombocytopenia	TA+CA	3	1.15	0.83–1.60	30		4	1.41	0.53–3.74	0	
	TA+PL	1	1.35	0.39–4.67	—		1	1.44	0.06–36.38	—	
	AN+CY	1	1.07	0.7–1.64	—		4	0.64	0.41–1.02	0	
	PY+AN+CY	0	—	—	—	0.925	1	2.09	0.19–23.56	0	0.415
	TA+X	4	1.17	0.85–1.6	0		5	1.41	0.55–3.59	0	
	AN+Y	1	1.07	0.70–1.64	—	0.750	5	0.67	0.43–1.05	0	0.162
	TA/AN+X/Y	5	1.13	0.88–1.46	0	0.344	10	0.77	0.52–1.15	0	0.206
Infection/febrile neutropenia	TA+CA	3	1.92	1.10–3.35			4	2.78	0.92–8.43	46.3	
	TA+PL	1	2.45	0.27–22.6			1	2.44	0.11–52.43	—	
	AN+CY	0	—	—			4	2.36	1.03–5.43	84.8	
	PY+AN+CY	0	—	—			2	8.18	1.35–49.63	46.8	0.677
	TA+X	4	1.95	1.14–3.35	0		5	2.55	1.02–6.39	28.3	
	AN+Y	0	—	—			6	3.08	1.50–6.31	80.4	0.753
	TA/AN+X/Y	4	1.95	1.14–3.35	0	0.015	11	2.93	1.68–5.09	68.3	<0.001
Anorexia	TA+CA	1	1.23	0.74–2.05	—		2	0.56	0.13–2.38	0	
	TA+PL	1	1.22	0.47–3.16	—		1	1.44	0.06–36.38	—	
	AN+CY	1	1.15	0.79–1.69	—		1	3.9	1.42–10.71	—	
	PY+AN+CY	0	—	—	—	0.979	1	1.89	0.53–6.76	—	0.195
	TA+X	2	1.23	0.78–1.92	0		3	0.66	0.18–2.40	—	
	AN+Y	1	1.15	0.79–1.69	—	0.838	2	3.02	1.38–6.6	—	0.048
	TA/AN+X/Y	3	1.18	0.88–1.58	0	0.26	5	2.04	1.08–3.88	16	0.029
Stomatitis/mucosal inflammation	TA+CA	2	0.74	0.51–1.07	0		1	0.41	0.03–4.82	—	
	TA+PL	0	—	—	—		0	—	—	—	
	AN+CY	1	1.57	1.07–2.31	—		5	1.5	0.99–2.27	44.2	
	PY+AN+CY	0	—	—	—	0.006	2	0.92	0.04–22.50	72.8	0.619
	TA+X	2	0.74	0.51–1.07	0		1	0.41	0.03–4.82	—	
	AN+Y	1	1.57	1.07–2.31	0	0.006	7	1.49	1.01–2.19	44.3	0.312
	TA/AN+X/Y	3	0.95	0.53–1.70	75.8	0.850	8	1.44	0.98–2.10	40.6	0.063
Nausea	TA+CA	1	1.91	1.23–2.98	—		2	1.17	0.3–4.5	0	
	TA+PL	1	2.49	0.99–6.24	—		1	1.72	0.33–8.85	—	
	AN+CY	1	0.58	0.38–0.88	—		3	1.04	0.44–2.45	46.7	
	PY+AN+CY	0	—	—	—	<0.001	2	1.07	0.53–2.15	0	0.962
	TA+X	2	2.01	1.35–2.99	0		3	1.38	0.49–3.85	0	

		I–IV					III–IV				
Safety Endpoints	Group	No. of Studies	HR	CI	I^2	P	No. of Studies	HR	CI	I^2	P
	AN+Y	1	0.58	0.38–0.88	—	<0.001	5	1.08	0.7–1.69	0	0.676
	TA/AN+X/Y	3	1.34	0.52–3.44	88.8	0.546	8	1.13	0.75–1.69	0	0.566
Vomiting	TA+CA	2	1.56	1.09–2.25	0		3	0.45	0.12–1.6	0	
	TA+PL	1	1.10	0.44–2.76	—		1	0.93	0.08–10.72	—	
	AN+CY	1	0.58	0.40–0.85	—		5	0.66	0.47–0.92	12.3	
	PY+AN+CY	0	—	—	—	0.001	2	0.63	0.30–1.30	0	0.936
	TA+X	3	1.49	1.06–2.09	0		4	0.52	0.17–1.57	0	
	AN+Y	1	0.60	0.40–0.85	0	<0.001	7	0.65	0.48–0.88	0	0.698
	TA/AN+X/Y	4	1.09	0.61–1.98	79	0.764	11	0.64	0.48–0.86	0	0.003
Diarrhea	TA+CA	2	0.59	0.4–0.86	24.7		3	0.14	0.03–0.63	0	
	TA+PL	1	6.8	0.37–125.03	—		0			—	
	AN+CY	1	4.96	3.13–7.85	—		3	5.67	2.05–15.69	0	
	PY+AN+CY	0	—	—	—	<0.001	1	5.29	0.25–112..22	0	<0.001
	TA+X	3	0.71	0.36–1.41	50.6		3	0.14	0.03–0.63	0	
	AN+Y	1	4.96	3.13–7.85	50.6	0.001	4	5.63	2.14–14.79	0	<0.001
	TA/AN+X/Y	4	1.60	0.39–6.49	94.2	0.511	7	1.14	0.24–5.37	64.5	0.865
Hand–foot syndrome	TA+CA	3	0.11	0.07–0.17	0	<0.001	4	0.05	0.01–0.21	0	<0.001
Sensory neuropathy	TA+CA	3	0.6	0.39–0.91	0		2	2.14	0.47–9.7	0	
	TA+PL	0	—	—	—		0			—	
	AN+CY	1	5.69	3.06–10.56	0		3	5.66	1.93–16.54	0	
	PY+AN+CY	0	—	—	—	<0.001	2	5.17	0.60–44.70	0	0.578
	TA+X	3	0.60	0.39–0.91	0		2	2.14	0.47–9.7	0	
	AN+Y	1	5.68	3.06–10.56	—	<0.001	5	5.56	2.13–14.53	0	0.296
	TA/AN+X/Y	4	1.04	0.28–3.81	91.6	0.958	7	4.40	1.98–9.78	0	<0.001

AN+CY = anthracyclines+cyclophosphamide, AN+Y = anthracycline-based combination regimens, CI = confidence interval, HR = hazard ratio, PY+AN+CY = anthracyclines + 5-fluorouracil + cyclophosphamide, TA/AN+X/Y = taxane-based + anthracycline-based combination regimens, TA+CA = taxanes + capecitabine, TA+PL = taxanes + platinum, TA+X = taxane-based combination regimens. Each adverse event is reported with a risk ratio (95% CI) and statistical signicance. *P* values of subgroup differences or total.

based combined regimens are probably inappropriate for treating MBC patients. As previously reported, the incidences of grades 1–4 and 3–4 gastrointestinal and hematological toxicities were significantly higher among patients receiving combined taxanes and anthracyclines. Additionally, combined therapy with taxanes and capecitabine yielded the same results in terms of the HRs for ORR, DCR, TTP, and OS, and showed a better adverse event profile.

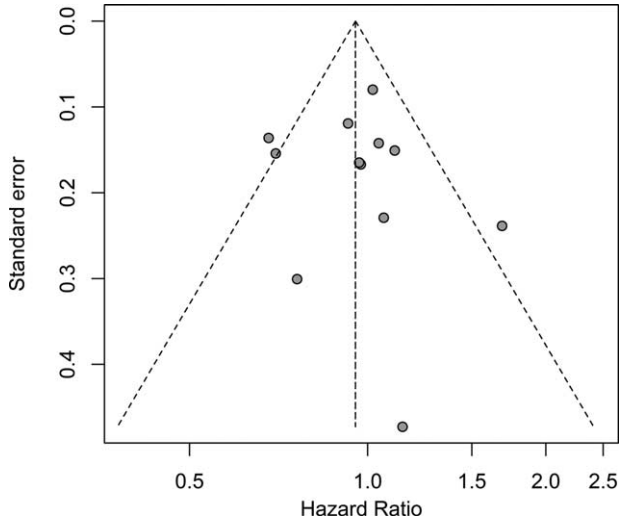

FIGURE 3. Funnel plot for assessing publication bias.

A possible limitation of this meta-analysis is that it used information obtained from published data rather than individual patient information. However, our analysis included clinical trials conducted with patients having advanced or metastatic disease, and were thus highly comparable in terms of their prognosis. Even after considering its limitations, our analysis underlines the fact that none of the previously described regimens can be considered a ''Gold Standard'' for treating MBC.

In recent years, a variety of clinical trials have been conducted in hopes of showing improved patient survival; however, their rationales were rarely based on preclinical findings. If preclinical findings were used to justify examining new treatment regimens, the results might be of great interest. Gemcitabine, a pyrimidine antimetabolite, has potential for use in combination therapy because of its unique mechanism of action and toxicity profile that do not overlap those of non-anthracycline-based treatments.[35] Numerous studies have examined the efficacy and safety of gemcitabine when used in combination with paclitaxel, carboplatin, or cisplatin in patients with advanced MBC.[36–38]

Xu et al[39] reported results of a multicenter, open-label, randomized, parallel, Phase II selection trial that enrolled patients previously treated with anthracycline-based neoadjuvant or adjuvant chemotherapy. That study found no significant differences regarding OS and PFS between patients treated with combined gemcitabine and paclitaxel versus gemcitabine along with platinum. Additionally, the 2 gemcitabine-based therapies

showed similar activity and tolerability. Finally, because gemcitabine and platinum produce similar patient survival results but have different toxicity profiles, gemcitabine–platinum regimens may be further evaluated in MBC patients who fail anthracycline treatment.[39]

Recently, the efficacy of oral vinorelbine when used as a single agent has been evaluated in cases of MBC, and additional preliminary evidence suggests that vinorelbine increases the activity of other combined therapies, making them suitable for further clinical testing.[40,41] Campone et al[42] mentioned the importance of oral vinorelbine-based treatments in therapy for advanced breast cancer,[42] and oral vinorelbine along with capecitabine regimens were compared with docetaxel with capecitabine regimens in a randomized, active control, parallel group, multicenter, Phase II study. The results showed that combinations of oral vinorelbine and capecitabine and combinations of docetaxel and capecitabine had equivalent efficacies but different toxicity profiles. Combined vinorelbine and capecitabine treatment resulted in lower incidences of neutropenia, infection, hand–foot syndrome, fatigue/asthenia, and alopecia, whereas combined docetaxel and capecitabine regimens produced fewer gastrointestinal events. Combined therapy with vinorelbine and capecitabine represents an alternative to combined docetaxel and capecitabine for MBC patients previously treated with anthracycline in a (neo)adjuvant setting, and offers the advantages associated with a totally oral treatment regimen.[43]

An increased interest in pemetrexed-based treatment of MBC has resulted in its use in Phase I–II trials. Pemetrexed, a multitargeted antifolate, has been shown to inhibit thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, and has demonstrated antitumor activity in multiple types of solid cancers.[44] Additionally, a single administration of pemetrexed has demonstrated activity in several Phase II studies of patients with advanced breast cancer,[45] suggesting that high rates of efficacy may be obtained by its combined use with cyclophosphamide. Dittrich C et al investigated the efficacy and safety of a combined pemetrexed and cyclophosphamide regimen in a recent Phase II trial and reported a satisfactory toxicity profile and high antitumor activity.[45]

CONCLUSION

This meta-analysis was not conducted to modify current clinical practice, but rather to reevaluate current treatment options and make suggestions for future prospective trials. Our statistical results suggest that patients with MBC should be treated with taxane-based combination regimens, and especially with a combination of taxanes and capecitabine. Compared with the patients treated with combined anthracycline with taxane regimens, patients treated with taxanes along with capecitabine realized the same benefits in terms of TTP, OS, ORR, and DCR, but experienced fewer hematological and gastrointestinal toxicities. In the era of nontaxane and nonanthracycline-based combination therapies, novel approaches based on verified preclinical findings, a more rational use of currently available drugs, and an improved method for selecting patients may be needed to address this topic.

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