BMC Women's Health

RESEARCH

Open Access

Comparison of the efficacy and safety of docetaxel plus capecitabine versus docetaxel plus epirubicin for human epidermal growth factor 2 -negative breast cancer: a meta-analysis

Jie Wu[1*], Zhiqiang Wang[2] and Yi Fu[3]

Abstract

Background This study aimed to evaluate the efficacy and safety of docetaxel plus capecitabine (TX) and docetaxel plus epirubicin (TE) in the treatment of human epidermal growth factor 2 (HER2)-negative breast cancer.

Methods Relevant studies assessing the efficacy and safety of TX versus TE were systematically searched from PubMed, Cochrane Library, Embase, and Web of Science databases until February 6, 2025. Progression-free survival (PFS), and clinical response, including the overall response rate (ORR), disease control rate (DCR), and grade 3/4 adverse events were compared.

Results Four articles with moderate methodological quality were included. The pooled results revealed no significant differences in PFS (hazard ratio [HR] (95% confidence interval CI) = 0.86 (0.70, 1.05), $P = 0.14$), ORR (risk ratio [RR] (95%CI) = 1.02 (0.92, 1.14), $P = 0.71$), or DCR (RR (95%CI) = 1.02 (0.92, 1.14), $P = 0.71$) between the TX and TE groups. For grade 3/4 adverse events, only the combined results for neutropenia (RR (95%CI), 0.71 (0.52, 0.95); $P = 0.02$) and hand-foot syndrome (RR (95%CI) = 14.36 (3.45, 59.84); $P = 0.0003$) demonstrated significant differences between the two groups. No significant differences were observed in other adverse events, including febrile neutropenia, anemia, thrombocytopenia, nail/hair toxicity, hepatic toxicity, diarrhea, nausea, vomiting, infection, asthenia, and neuropathy.

Conclusion In patients with HER2-negative breast cancer, TX and TE have comparable survival benefits and efficacy. However, TX exhibits a reduced incidence of neutropenia, but a higher likelihood of hand-foot syndrome than that observed in TE.

Highlights

- Four articles with moderate methodological quality were included.
- TX and TE have similar efficacy in patients with HER2-negative breast cancer.
- TX could reduce the risk of neutropenia compared to TE.

*Correspondence:
Jie Wu
jiewu82@sjtu.edu.cn

Full list of author information is available at the end of the article

- TX increased the risk of hand-foot syndrome compared to that observed with TE.

Keywords HER2-negative breast cancer, Docetaxel, Capecitabine, Epirubicin, Efficacy, Safety, Meta-analysis

Background

Breast cancer is the most prevalent malignancy in women and poses a substantial global health burden. Approximately 2.3 million new cases have been reported, with an estimated 685,000 deaths attributed to this disease in 2020 [1]. Currently, treatment alternatives for breast cancer, especially metastatic triple-negative breast cancer, are limited, with cytotoxic chemotherapy being the mainstay approach in clinical practice [2]. The use of (neo)adjuvant chemotherapy has a remarkable impact on reducing the risk of breast cancer recurrence and significantly improving the overall survival rates among patients [3]. For individuals with human epidermal growth factor 2 (HER2)-negative breast cancer, particularly those with locally advanced breast cancer, the combination of taxanes and anthracyclines is widely recommended as the preferred treatment approach [4]. However, anthracycline-containing chemotherapy is associated with multiple adverse events including emesis/vomiting, myelosuppression, heart failure, myelodysplasia, and treatment-related leukemia [5–7]. Therefore, the toxicity profile of these regimens has become a critical consideration within the decision-making framework for (neo)adjuvant therapy, prompting researchers to investigate alternative treatment strategies.

Capecitabine, an oral prodrug of fluorouracil, has been demonstrated to exhibit high efficacy in the management of breast cancer [8–10]. Several studies have demonstrated that a first-line regimen of docetaxel combined with capecitabine (TX) is more effective than docetaxel alone, confirming the application of the modality as a first-line treatment for advanced breast cancer [11, 12]. Several studies have compared the efficacy and safety of TX and docetaxel plus epirubicin (TE) for breast cancer treatment. However, the sample size of these studies was relatively small, and the differences in efficacy between the two regimens remain unclear [13–15].

To obtain comprehensive and objective results, we performed a meta-analysis to pool the data from relevant clinical studies. The objective of this meta-analysis was to compare the efficacy and safety of the TX and TE regimens in the treatment of HER2-negative breast cancer.

Methods

Search strategy

According to the predetermined search strategy, relevant studies were retrieved from the PubMed, Cochrane Library, Embase, and Web of Science databases. The search keywords included docetaxel, Taxotere, capecitabine, xeloda, epirubicin, farmorubicin, breast neoplasms, breast cancer, and breast carcinoma. Keywords within the same category were combined using "OR", whereas keywords from different categories were combined using "AND". Subject and free words were combined for the search, and the search strategy for each database was adjusted according to its characteristics (Supplementary Tables 1–4). The search was conducted until February 6, 2025, without language restrictions. Additionally, we manually screened the references of the included studies and relevant reviews to obtain additional studies suitable for meta-analysis.

Study screening

The inclusion criteria for study selection were: (1) patients with HER2-negative breast cancer; (2) studies comparing the outcomes of TX and TE in the treatment of breast cancer; (3) randomized controlled trials (RCTs) or non-RCTs; and (4) studies including one or more of the following outcomes: progression-free survival (PFS), clinical responses including overall response rate (ORR) and disease control rate (DCR), as well as grade 3/4 adverse events. The exclusion criteria were: (1) studies with the concomitant use of other medications (2) reviews, conference abstracts, comments, and other non-authoritative studies; and (3) repeated publications or multiple articles using the same data. These articles were excluded except the one with the most complete research information. Based on these criteria, two investigators independently conducted screening.

Data extraction

Using a predesigned standardized form, two investigators independently completed the data extraction. The information extracted included the first author, publication year, basic characteristics of the study participants (age and sample size), diagnostic criteria and staging of breast cancer, study type, treatment history, and outcomes. After completing the data extraction, the forms were exchanged and reviewed, and any inconsistencies were resolved through discussion.

Quality assessment

For non-RCTs, the risk of bias in non-randomized studies of interventions (ROBINS-I) [16] was used to evaluate the methodological quality. For RCTs, the Cochrane Collaboration's tool for estimating risk [17] was utilized.

Statistical analysis

The differences in PFS between the TX and TE groups were compared using hazard ratios (HR) and 95%

confidence intervals (CI) as effect measures. To compare other study outcomes, risk ratios (RR) and 95% CI were employed as effect measures. Owing to the considerable clinical and methodological heterogeneity among the included studies, a random-effects model was employed for meta-analysis. Heterogeneity was assessed using Cochran's Q and I^2 test [18]. If $P < 0.1$ or $I^2 > 50\%$, significant heterogeneity was detected. However, if $P \geq 0.1$ and $I^2 \leq 50\%$, no significant heterogeneity was observed. The statistical analyses described above were performed using the RevMan 5.3 software (RevMan, Copenhagen, Denmark).

Assessment of the quality of evidence

The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method using the GRADEpro GDT online tool. The rating process followed the GRADE Handbook and guidelines [19, 20].

Results

Selection of included studies

Following the search strategy, 469 articles were retrieved from electronic databases. After removing 151 duplicates, 311 articles were excluded following a review of their titles and abstracts. Subsequently, seven articles were subjected to full-text reading, meanwhile, three were excluded. No additional studies were identified through the manual search. Finally, four articles [13–15, 21] were included. The study search process is illustrated in Fig. 1.

Description of included studies

Table 1 presents the characteristics of the included studies. Among the four included studies, three were RCTs and one was a retrospective clinical study. The participants in all included studies were patients with HER2-negative breast cancer confirmed by pathology, histology, or cytology. Except for the study conducted by Yang et al. [15], which included patients with stages 2 and 3 breast cancer, the remaining studies included patients with advanced-stage breast cancer.

During the recruitment of patients with breast cancer, all the included studies excluded those with abnormal cardiac, hematological, hepatic, or renal function. Three studies focused on first-line treatments, whereas one examined neoadjuvant therapy. The dose of capecitabine in the study conducted by Mavroudis et al. [13] was 50 mg/m^2 lower than that in other studies (950 vs. 1000 mg/m^2); however, the use of epirubicin and docetaxel (dose, frequency, and cycles) was consistent across all included studies.

The sample size of the included studies varied from 68 to 272 cases, totaling 545 patients (269 in the TX group and 276 in the TE group). Two groups were comparable in terms of age, Eastern Cooperative Oncology Group Performance Status score, and history of radiotherapy or (neo)neoadjuvant chemotherapy. However, a significant difference was noted in the history of adjuvant endocrine therapy in the study by Bachelot et al. [21], whereas the differences were not significant in the remaining three studies.

Assessment of study quality

The results of the quality assessment of the RCTs are displayed in Supplementary Fig. 1. The included studies did not provide information on the blinding procedures, and most did not report specific randomization and allocation concealment schemes. Therefore, selection, performance, and detection had a moderate risk of bias. The quality assessment results for the non-RCTs are demonstrated in Supplementary Table 5. This study exhibited a moderate or uncertain level of bias in terms of participant selection, intervention, and outcome measurements. Overall, the included studies were of moderate quality.

Analysis of PFS

Three studies reported PFS in the TX and TE groups, and significant heterogeneity was observed ($I^2 = 41\%$, $P = 0.18$). The pooled results were HR (95%CI) = 0.86 (0.70, 1.05) ($P = 0.14$) (Fig. 2), indicating that the two treatment regimens achieved similar PFS in patients with HER2-negative breast cancer.

Clinical response analysis

Clinical responses, including the ORR and DCR, were evaluated to compare the clinical efficacy of the two treatment regimens. The pooled results did not demonstrate a significant difference in ORR (RR (95%CI) = 1.02 (0.92, 1.14), $P = 0.71$) and DCR (RR (95%CI) = 1.02 (0.92, 1.14), $P = 0.71$) between the TX and TE groups (Fig. 3).

Analysis of grade 3/4 adverse events

Grade 3/4 adverse effects of the two treatment regimens were analyzed, including hematological (neutropenia, febrile neutropenia, anemia, and thrombocytopenia), toxicity (nail/hair toxicity and hepatic toxicity), digestive (diarrhea, nausea, and vomiting), and other effects (hand-foot syndrome, infection, asthenia, and neuropathy).

For hematological indicators, the combined results for neutropenia revealed statistical significance, with an RR (95%CI) of 0.71 (0.52, 0.95) ($P = 0.02$). This result confirmed that TX reduced the risk of neutropenia compared to the risk observed with TE. However, the combined results for the other three indicators were not statistically significant ($P > 0.05$) (Fig. 4). Moreover, only the studies reporting febrile neutropenia demonstrated substantial heterogeneity ($I^2 = 73\%$, $P = 0.06$).

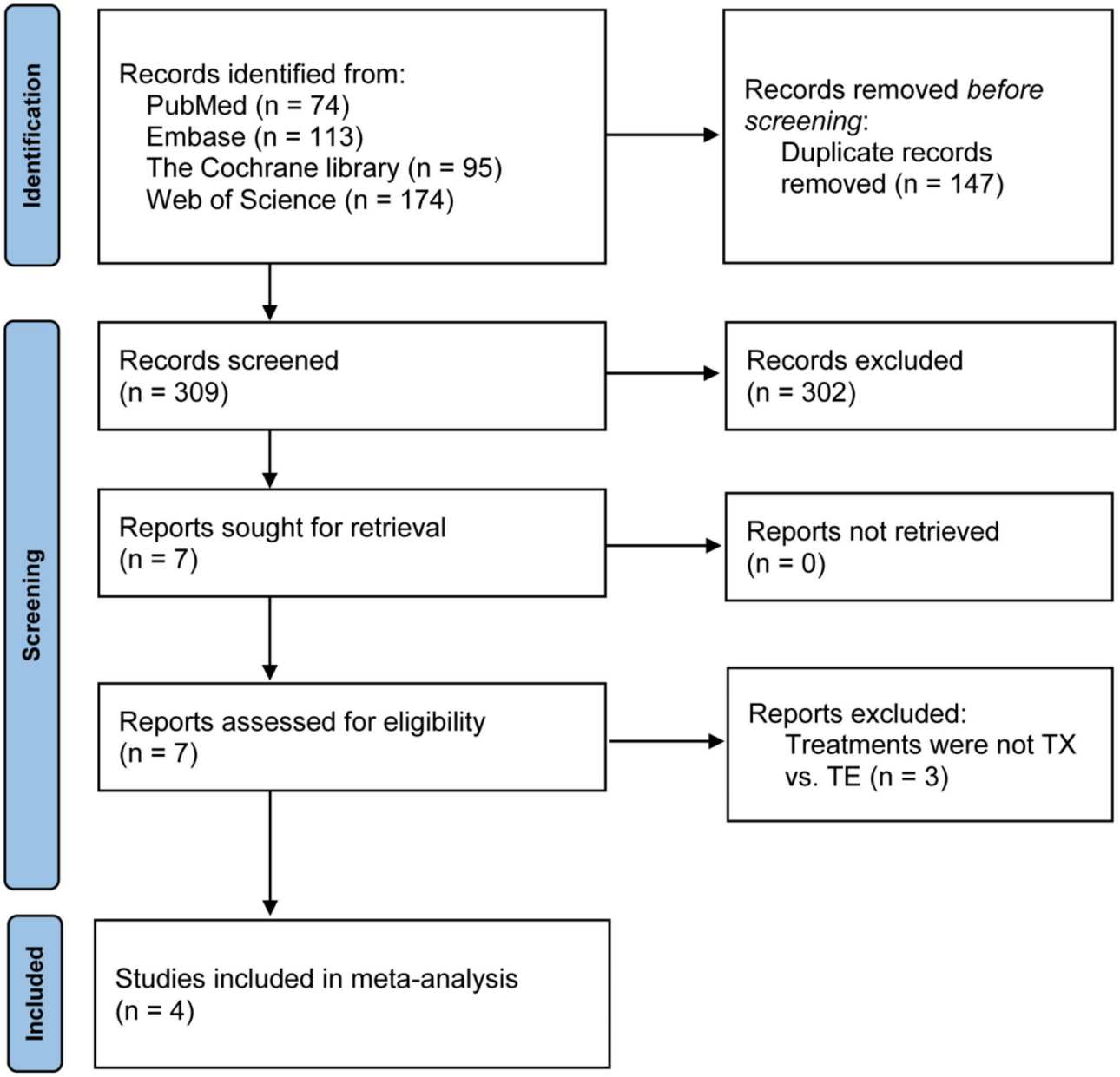

Fig. 1 The study search results and the process of study selection

No significant heterogeneity was detected among the studies reporting the indicators of toxicity and digestive side effects. The pooled results for nail/hair and hepatic toxicities were RR (95%CI) = 4.38 (0.76, 25.20) (P = 0.10) (Nail/hair toxicity) and RR (95%CI) = 3.04 (0.32, 28.64) (P = 0.33), respectively (Fig. 5). The pooled results for diarrhea, nausea, and vomiting were RR (95%CI) = 2.70 (0.85, 8.62) (P = 0.09), RR (95%CI) = 0.79 (0.26, 2.42) (P = 0.68), and RR (95%CI) = 1.08 (0.33, 3.51) (P = 0.90), respectively (Fig. 6). These results demonstrate that the two treatment regimens caused similar toxicity and digestive side effects in patients with HER2-negative breast cancer.

We also analyzed differences in hand-foot syndrome, infection, asthenia, and neuropathy between the two treatment regimens. However, only the pooled results for hand-foot were statistically significant (RR (95%CI) = 14.36 (3.45, 59.84); P = 0.0003) (Fig. 7). The studies included for these four indicators did not demonstrate significant heterogeneity (I^2 = 0%, $P > 0.1$).

Certainty of evidence

According to the GRADE assessment, the certainty of evidence for febrile neutropenia, nail/hair toxicity, hepatic toxicity, and hand-foot syndrome was low,

Table 1 Characteristics of the included studies in this meta-analysis

Study	Location	Design	Follow-up, months, median	Group	n	Age, years	ECOG PS, %, 0/1/2	Primary therapy		
								Radiotherapy,%	(Neo)adjuvant chemotherapy, %	Adjuvant endocrine therapy, %
Bachelot, T 2011	France	RCT	41.9	TX	33	57 (32–74)	33/61/6	76	58	70
				TE	35	59 (34–71)	32/65/3	63	54	43 *
Mavroudis, M 2010	Greece	RCT	43.8	TX	136	63.0 (31–75)	48.5/48.5/3.0	36.8	51.5	41.2
			39.8	TE	136	60.5 (30–75)	55.1/42.6/2.2	38.2	40.4	35.3
Yang, B 2013	China	RCS	NR	TX	46	48.0±7.5	41/5, 0–1/2	47.8	71.7	54.3
				TE	46	46.4±10.1	43/3, 0–1/2	52.2	65.2	43.4
Yang, HP 2022	China	RCT	69	TX	54	33/21, >50, ≤50	NR	NR	NR	NR
				TE	59	25/34	NR	NR	NR	NR

ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reported; RCS, retrospective clinical study; RCT, randomized controlled trial; TE, docetaxel plus epirubicin; TX, docetaxel plus capecitabine

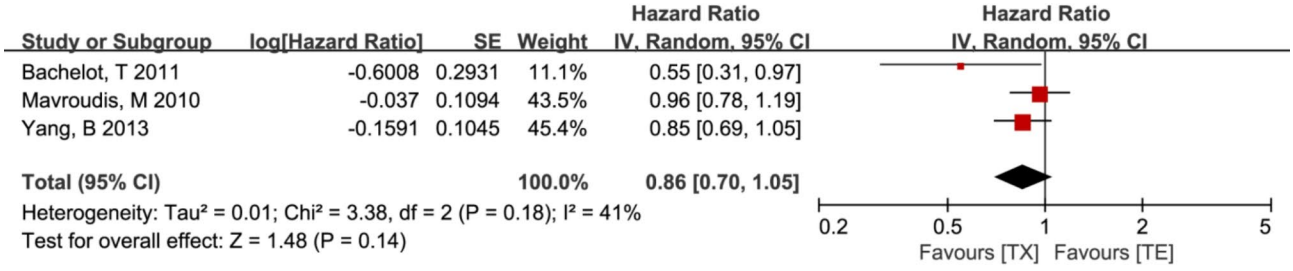

Fig. 2 Forest plots illustrate the pooled results for progression-free survival between docetaxel plus capecitabine and docetaxel plus epirubicin

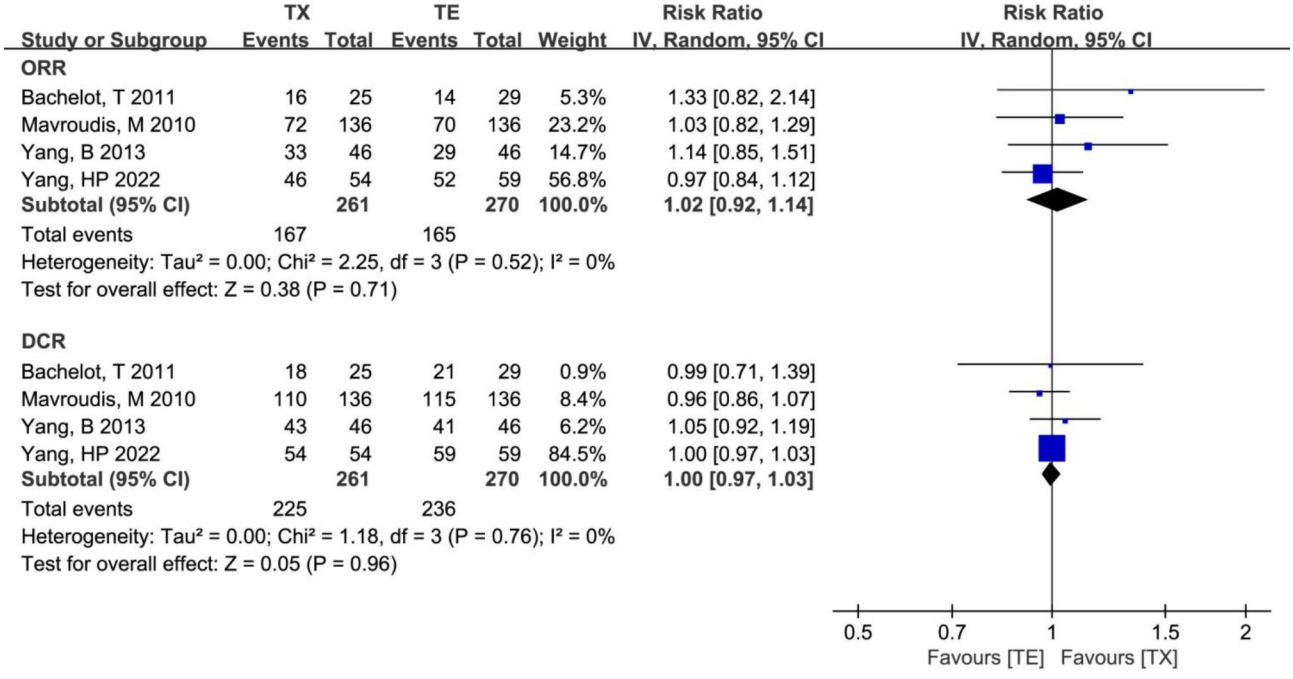

Fig. 3 Forest plots demonstrate the pooled results for the overall response rate and disease control rate between docetaxel plus capecitabine and docetaxel plus epirubicin

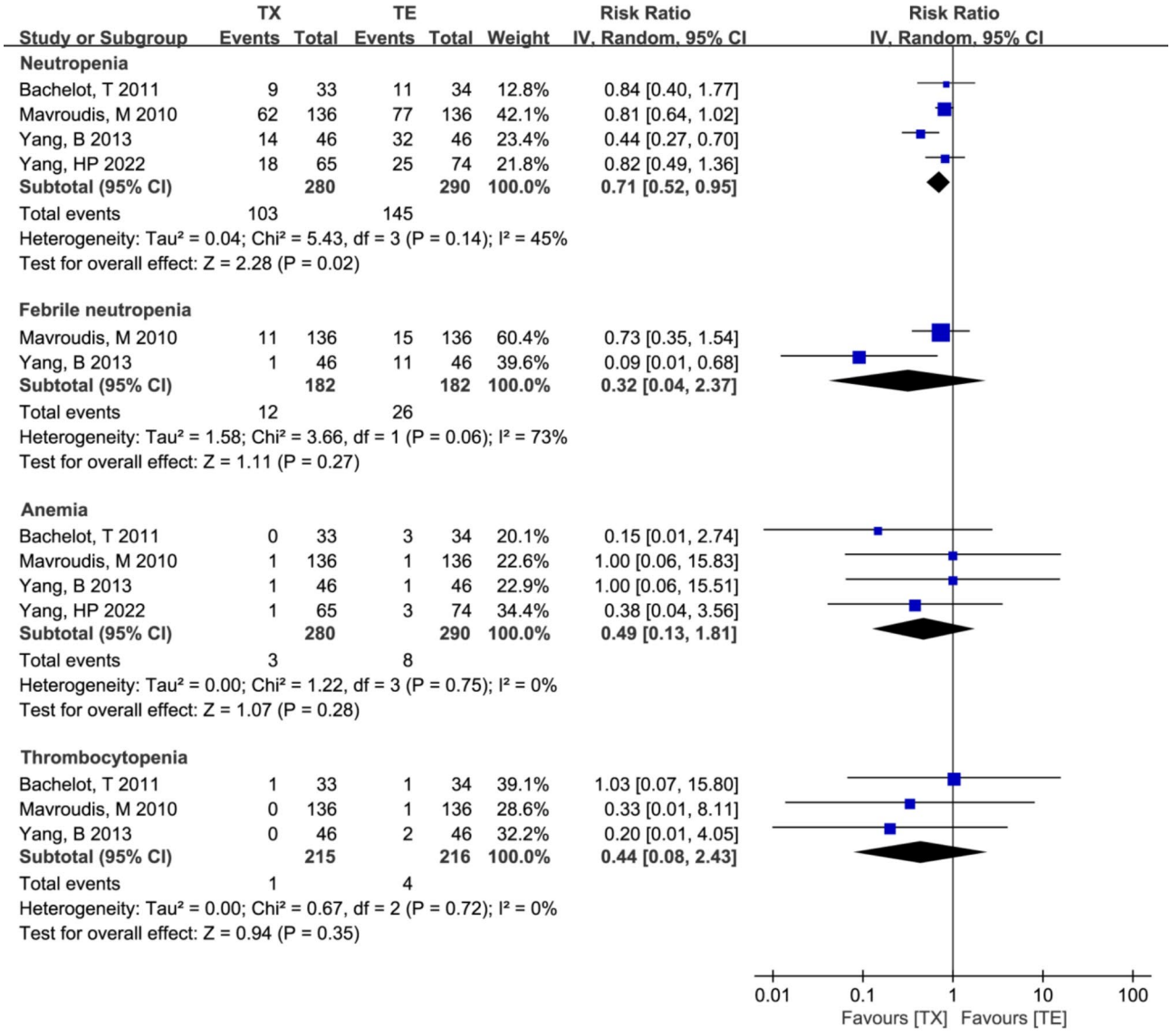

Fig. 4 Forest plots reveal the pooled results for neutropenia, febrile neutropenia, anemia, and thrombocytopenia between docetaxel plus capecitabine and docetaxel plus epirubicin

whereas that for the other outcome indicators was moderate (Supplementary Table 6).

Discussion

Clinically, HER2-negative breast cancer is not typically managed with HER2-targeted therapy [22, 23]. Therefore, exploring optimal treatment regimens is crucial for improving the outcomes of patients with HER2-negative breast cancer. In this meta-analysis, we compared the efficacy and safety of the TX and TE regimens in patients with HER2-negative breast cancer. Our data did not support the superior clinical efficacy or survival benefits of TX compared to those of TE. However, TX reduced the risk of neutropenia and increased that of hand-foot syndrome.

Capecitabine is effective and well-tolerated in the treatment of metastatic breast cancer [11, 24]. The previous ERASME-4 study revealed that the 6-month non-progression rates of the TX and TE regimens were 75.8% and 65.7% (P = 0.36), respectively. Furthermore, the median PFS was 12.4 and 6.8 months (P = 0.04), respectively, indicating that first-line TX may be an alternative to TE. However, since this was a phase 1 clinical study, the conclusion lacked sufficient strength [21]. A recent randomized multicenter phase II trial also revealed that TX and TE regimens had comparable pathological complete response and long-term survival rates. Nevertheless, the sample size of this study was small and the statistical analysis was insufficient [14]. This meta-analysis aimed to provide updated evidence. We discovered that the TX

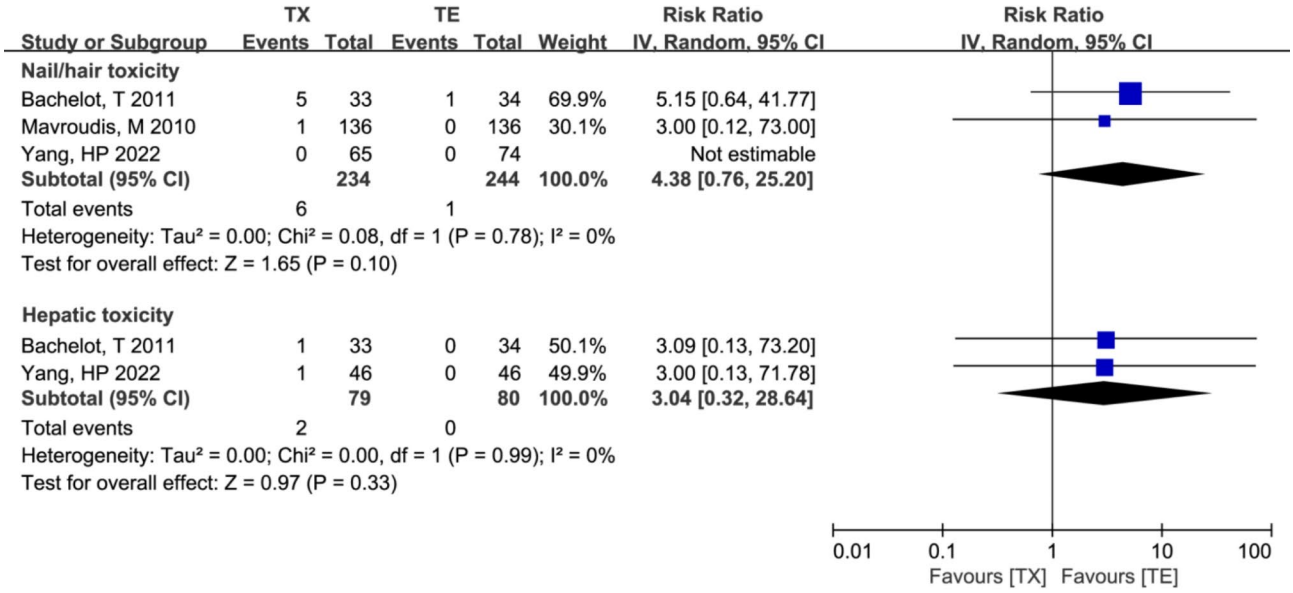

Fig. 5 Forest plots illustrate the pooled results for nail/hair toxicity and hepatic toxicity between docetaxel plus capecitabine and docetaxel plus epirubicin

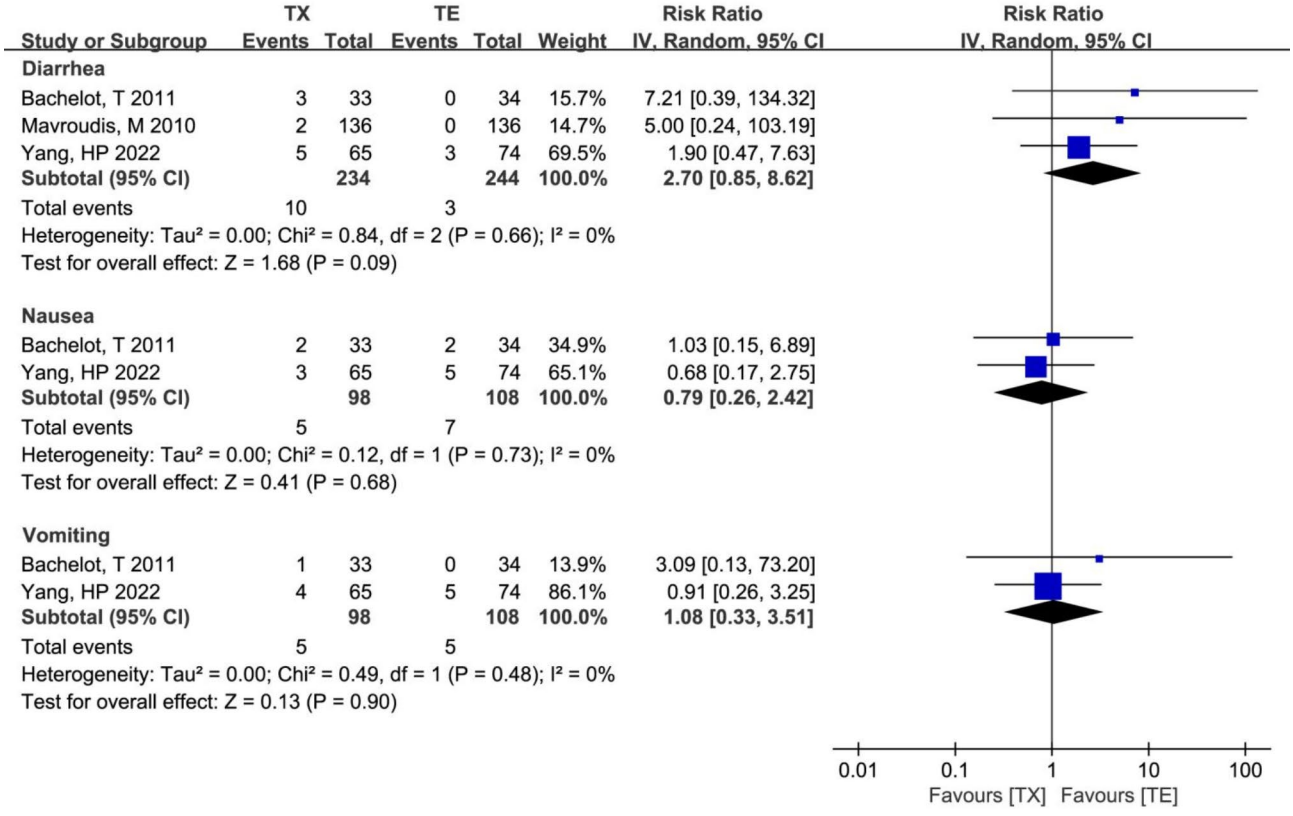

Fig. 6 Forest plots demonstrate the pooled results for diarrhea, nausea, and vomiting between docetaxel plus capecitabine and docetaxel plus epirubicin

and TE regimens achieved similar PFS rates (HR (95%CI) = 0.86 (0.70, 1.05), P = 0.14). The ORR (RR (95%CI) = 1.02 (0.92, 1.14), P = 0.71) and DCR (RR (95%CI) = 1.02 (0.92, 1.14), P = 0.71) indicated comparable efficacy and survival benefits between the two regimens. The dose-dense regimens have been reported to be effective for hormone receptor-negative breast cancers [25, 26]. The integration of capecitabine into standard agent regimens was effective in addressing HER2-negative breast cancer, with daily administration of capecitabine offering

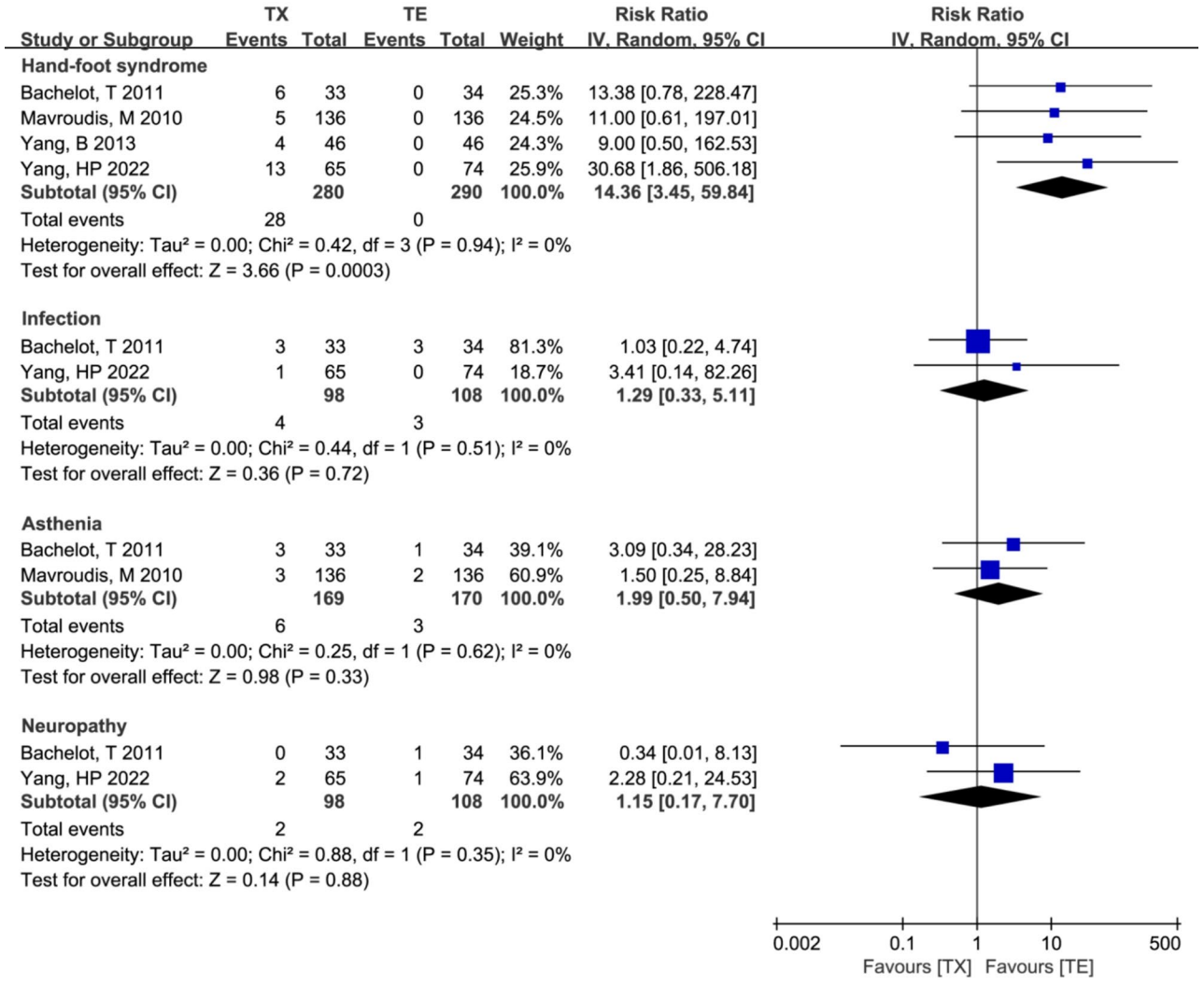

Fig. 7 Forest plots display the pooled results for hand-foot syndrome, infection, asthenia, and neuropathy between docetaxel plus capecitabine and docetaxel plus epirubicin

several potential benefits, including intensifying chemotherapy, prolonging cancer exposure to fluorouracil compared with intravenous administration, and increasing intratumoral concentrations of fluorouracil [27].

Treatment-related adverse events are common concerns for patients undergoing therapy [28, 29]. From a safety perspective, we compared the risk of adverse events including neutropenia, febrile neutropenia, anemia, thrombocytopenia, nail/hair toxicity, hepatic toxicity, diarrhea, nausea, vomiting, hand-foot syndrome, infection, asthenia, and neuropathy. An increased incidence of hand-foot syndrome after TX treatment was reported in a previous trial investigating metastatic disease [24], which is associated with the characteristics of capecitabine and is difficult to avoid. Additionally, TX caused less grade 4 neutropenia than that reported with TE, which is consistent with previous findings [21]. Except for neutropenia and hand-foot syndrome, no differences were observed in the other indicators between the two regimens.

This study has several advantages. First, to the best of our knowledge, this is the first meta-analysis to compare the outcomes of TX and TE in the treatment of HER2-negative breast cancer. Second, the methodological quality of the included studies was assessed as moderate, with a low risk of bias for items, such as loss to follow-up and reporting bias. Third, the statistical heterogeneity of most outcome indicators was relatively low, indicating a high consistency in the effect sizes. Finally, the included studies displayed minor disparities in the study population and intervention protocols, suggesting good generalizability of the meta-analysis results. Despite these advantages, this study has certain limitations. First, due to the limited number of included studies, assessing the impact of factors such as region, study type, cancer stage, and age on the results through a subgroup analysis

or meta-regression was not feasible. Second, the small sample size may have limited statistical power to detect significant differences in outcomes and explain the statistical variations in the intervention protocols. Finally, potential selection, performance, and detection biases were present in the included studies, which also affected the quality of the pooled results (the GRADE assessment results were low and moderate). However, the results of the meta-analysis still provide clinical reference values. Overall, we recommend that high-quality RCTs be conducted to explore the efficacy and safety of the two treatment regimens.

Conclusion

The findings suggest that TX and TE may provide similar survival benefits and efficacy in patients with HER2-negative breast cancer. TX is likely to have a lower risk of neutropenia than the risk associated with TE but a higher risk of hand-foot syndrome. In clinical practice, an optimal drug regimen can be tailored to the specific needs of individual patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-025-03628-z.

Supplementary Material 1

Supplementary Material 2

Acknowledgements
Not applicable.

Author contributions
Jie Wu carried out the conception and design of the research, Jie Wu and Zhiqiang Wang participated in the acquisition of data. Jie Wu, Yi Fu and Zhiqiang Wang carried out the analysis and interpretation of data. Jie Wu and Yi Fu performed the statistical analysis. Jie Wu conceived of the study, and participated in its design and coordination and drafted the manuscript and revision of manuscript for important intellectual content. All authors read and approved the final manuscript.

Funding
This study did not receive funding from any sources.

Data availability
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Key Laboratory of Hydrodynamics (Ministry of Education), School of Ocean and Civil Engineering, Shanghai Jiao Tong University, No.800 Dongchuan Road, Minhang District, Shanghai 200240, China
[2]Department of General Surgery, Tongren Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200336, China
[3]Shanghai Key Laboratory of Molecular Imaging, Collaborative Innovation Center for Biomedicines & School of Medical Instruments, Shanghai University of Medicine & Health Sciences, Shanghai 201318, China

Received: 18 November 2024 / Accepted: 21 February 2025
Published online: 07 March 2025

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin. 2021;71(3):209–49.
2. Caputo R, Buono G, Piezzo M, Martinelli C, Cianniello D, Rizzo A, Pantano F, Staropoli N, Cangiano R, Turano S, et al. Sacituzumab Govitecan for the treatment of advanced triple negative breast cancer patients: a multi-center real-world analysis. Front Oncol. 2024;14:1362641.
3. Sonnenblick A, Piccart M. Adjuvant systemic therapy in breast cancer: quo vadis? Ann Oncol. 2015;26(8):1629–34.
4. Network NCC. Sep: Breast Cancer (version 6.2021). https://www.nccnorg/professionals/physician_gls/pdf/breastpdf:Accessed 9 2021.
5. Group EBCTC. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. Lancet. 2012;379(9814):432–44.
6. Swain SM, Tang G, Geyer CE Jr, Rastogi P, Atkins JN, Donnellan PP, Fehrenbacher L, Azar CA, Robidoux A, Polikoff JA. Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. J Clin Oncol. 2013;31(26):3197.
7. Caparica R, Bruzzone M, Poggio F, Ceppi M, de Azambuja E, Lambertini M. Anthracycline and taxane-based chemotherapy versus docetaxel and cyclophosphamide in the adjuvant treatment of HER2-negative breast cancer patients: a systematic review and meta-analysis of randomized controlled trials. Breast Cancer Res Treat. 2019;174:27–37.
8. Von Minckwitz G, Rezai M, Fasching PA, Huober J, Tesch H, Bauerfeind I, Hilfrich J, Eidtmann H, Gerber B, Hanusch C. Survival after adding capecitabine and trastuzumab to neoadjuvant anthracycline-taxane-based chemotherapy for primary breast cancer (GBG 40—GeparQuattro). Ann Oncol. 2014;25(1):81–9.
9. Lluch A, Barrios CH, Torrecillas L, Ruiz-Borrego M, Bines J, Segalla J, Guerrero-Zotano Á, García-Sáenz JA, Torres R, de la Haba J. Phase III trial of adjuvant capecitabine after standard neo-/adjuvant chemotherapy in patients with early triple-negative breast cancer (GEICAM/2003-11_CIBOMA/2004-01). J Clin Oncol. 2020;38(3):203.
10. Muss HB, Polley M-YC, Berry DA, Liu H, Cirrincione CT, Theodoulou M, Mauer AM, Kornblith AB, Partridge AH, Dressler LG. Randomized trial of standard adjuvant chemotherapy regimens versus capecitabine in older women with early breast cancer: 10-year update of the CALGB 49907 trial. J Clin Oncol. 2019;37(26):2338.
11. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub J-P, Cervantes G, Fumoleau P, Jones S, Lui W-Y, Mauriac L. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 2002;20(12):2812–23.
12. Miles D, Vukelja S, Moiseyenko V, Cervantes G, Mauriac L, Van Hazel G, Liu W-Y, Ayoub J-P, O'Shaughnessy JA. Survival benefit with Capecitabine/docetaxel versus docetaxel alone: analysis of therapy in a randomized phase III trial. Clin Breast Cancer. 2004;5(4):273–8.
13. Mavroudis D, Papakotoulas P, Ardavanis A, Syrigos K, Kakolyris S, Ziras N, Kouroussis C, Malamos N, Polyzos A, Christophyllakis C. Randomized phase III trial comparing docetaxel plus epirubicin versus docetaxel plus capecitabine as first-line treatment in women with advanced breast cancer. Ann Oncol. 2010;21(1):48–54.
14. Yang H, Xu L, Guan S, Hao X, Ge Z, Tong F, Cao Y, Liu P, Zhou B, Cheng L. Neoadjuvant docetaxel and capecitabine (TX) versus docetaxel and epirubicin

(TE) for locally advanced or early her2-negative breast cancer: an open-label, randomized, multi-center, phase II trial. BMC Cancer. 2022;22(1):1357.
15. Yang B, Yang J, Shi W, Liu H, Zhu Y, Fang P, Ji T. Clinical paired study of comparing docetaxel plus capecitabine versus docetaxel plus epirubicin as first-line treatment in women with HER-2 negative advanced breast cancer. Zhonghua Yi Xue Za Zhi. 2013;93(18):1397–400.
16. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
17. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. 2008.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
19. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94.
20. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, Devereaux PJ, Montori VM, Freyschuss B, Vist G, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011;64(12):1283–93.
21. Bachelot T, Bajard A, Ray-Coquard I, Provencal J, Coeffic D, Agostini C, Boisseau M, Kaphan R, Dramais D, Oprea C. Final results of ERASME-4: a randomized trial of first-line docetaxel plus either capecitabine or epirubicin for metastatic breast cancer. Oncology. 2011;80(3–4):262–8.
22. Mazumder A, Shiao S, Haricharan S. HER2 activation and endocrine treatment resistance in HER2-negative breast cancer. Endocrinology. 2021;162(10):bqab153.
23. Li Y, Abudureheiyimu N, Mo H, Guan X, Lin S, Wang Z, Chen Y, Chen S, Li Q, Cai R. In real life, low-level HER2 expression May be associated with better outcome in HER2-negative breast cancer: a study of the National Cancer center, China. Front Oncol. 2022;11:774577.
24. Chan S, Romieu G, Huober J, Delozier T, Tubiana-Hulin M, Schneeweiss A, Lluch A, Llombart A, du Bois A, Kreienberg R. Phase III study of gemcitabine plus docetaxel compared with capecitabine plus docetaxel for anthracycline-pretreated patients with metastatic breast cancer. J Clin Oncol. 2009;27(11):1753–60.
25. Petrelli F, Cabiddu M, Coinu A, Borgonovo K, Ghilardi M, Lonati V, Barni S. Adjuvant dose-dense chemotherapy in breast cancer: a systematic review and meta-analysis of randomized trials. Breast Cancer Res Treat. 2015;151:251–9.
26. Bonilla L, Ben-Aharon I, Vidal L, Gafter-Gvili A, Leibovici L, Stemmer SM. Dose-dense chemotherapy in nonmetastatic breast cancer: a systematic review and meta-analysis of randomized controlled trials. J Natl Cancer Inst. 2010;102(24):1845–54.
27. Joensuu H, Kellokumpu-Lehtinen P-L, Huovinen R, Jukkola-Vuorinen A, Tanner M, Kokko R, Ahlgren J, Auvinen P, Lahdenperä O, Kosonen S. Adjuvant capecitabine in combination with docetaxel, epirubicin, and cyclophosphamide for early breast cancer: the randomized clinical FinXX trial. Jama Oncol. 2017;3(6):793–800.
28. Rizzo A, Santoni M, Mollica V, Logullo F, Rosellini M, Marchetti A, Faloppi L, Battelli N, Massari F. Peripheral neuropathy and headache in cancer patients treated with immunotherapy and immuno-oncology combinations: the MOUSEION-02 study. Expert Opin Drug Metab Toxicol. 2021;17(12):1455–66.
29. Guven DC, Erul E, Kaygusuz Y, Akagunduz B, Kilickap S, De Luca R, Rizzo A. Immune checkpoint inhibitor-related hearing loss: a systematic review and analysis of individual patient data. Supportive Care Cancer: Official J Multinational Association Supportive Care Cancer. 2023;31(12):624.

Publisher's note