Selection of breast cancer subtypes to improve benefits of intensive dose-dense chemotherapy: A systematic meta-analysis

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Abstract. Breast cancer (BC) is the most commonly diagnosed cancer and the second leading cause of cancer mortality among women worldwide. A large number of patients experience recurrence and BC-associated mortality following adjuvant chemotherapy. The present study aimed to determine the most suitable pathological subtype of BC to benefit from intensive dose-dense (DD) chemotherapy. A total of four electronic databases were searched from inception up to March 10, 2023. Randomized controlled trials (RCTs) and retrospective studies comparing DD chemotherapy with standard chemotherapy in patients with BC were included. Pairwise random effects and network meta-analyses were performed to summarize efficacy and safety outcomes. A total of 27 original studies including 27,580 patients with BC were included. In terms of efficacy, the present study evaluated overall survival, disease-free survival, event-free survival, recurrence-free survival, pathological complete response and objective remission rate. Significant differences were identified in overall, hormone receptor$^+$ (HR^+) and HR^- subgroups. Furthermore, from the network analysis, the HR^+ and $Her2^-$ subgroups had the highest ranking, and these findings suggested that $HR^+/Her2^-$ patients with BC should adhere to a treatment strategy including intensive DD chemotherapy, which is also characterized by an acceptable safety profile. In conclusion, patients with HR^+ and $Her2^-$ BC were revealed to be the most suitable pathological type and are most likely to benefit from intense DD chemotherapy. The present study was registered with PROSPERO, CRD2022420351567.

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Introduction

Breast cancer (BC) is the most commonly diagnosed cancer and the second leading cause of cancer death among women worldwide (1). Although adjuvant chemotherapy confers a one-third reduction in the 10-year risk of mortality from BC (2), a large number of patients will experience recurrence and BC-associated mortality (3). To improve the prognosis and sensitivity to chemotherapy of patients with BC, a new chemotherapy interval protocol has been proposed called intensive dose-dense (DD) chemotherapy, which consists of using the same chemotherapy agents and dosing but with shorter intervals between treatment cycles (4). Generally, the usual chemotherapy once every 3 weeks is shortened to once every 2 weeks to shorten the treatment time, improve the treatment effect, prolong the survival time of patients and improve the quality of life.

To the best of our knowledge, no studies have previously investigated which pathological type of patients is more suitable for DD chemotherapy. Zhu *et al* (5) revealed that patients with hormone receptor (HR)-positive (HR^+) BC treated with DD chemotherapy may benefit more from treatment (5). Lambertini *et al* showed that patients with $Her2^+$ BC receive less benefit under DD chemotherapy (6). Furthermore, the lack of an increased risk of serious adverse events with intensive chemotherapy for DD suggests that shorter chemotherapy intervals can be considered for follow-up treatments (7). Therefore, intensive DD chemotherapy may be more suitable for some patients.

However, the most suitable pathological BC subtype, including patients with HR^- or HR^+ BC, that is most responsive to DD chemotherapy remains to be identified. Currently, it is unknown whether intensive DD chemotherapy is beneficial for patients with different pathological subtypes. To the best of our knowledge, no previous systematic review (8-10) has provided a comprehensive overview using pairwise and network meta-analyses to evaluate which pathological type of BC is the most responsive to DD chemotherapy regimens. The present study aimed to determine the most suitable pathological subtype of BC to benefit from intensive DD chemotherapy.

Materials and methods

Protocol registration. The present network meta-analysis was conducted and reported following the Preferred Reporting Items

for Systematic Reviews and Meta-Analysis (PRISMA) (11) and the Cochrane Collaboration guidelines (12). This systematic review was registered with the PROSPERO online system as no. CRD2022420351567 (13).

Search strategy and eligibility criteria. The present study searched studies registered in PubMed(ncbi.nlm.nih.gov/pubmed), Web of Science(apps.webofknowledge.com), the Cochrane Library(www.cochranelibrary.com/) and China National Knowledge Infrastructure(https://www.cnki.net/)_ from the date of database inception to October 2022, and an upgraded search was conducted on March 10, 2023. The keywords 'breast cancer', 'intensive dose-dense chemotherapy' and their MeSH terms were used (see details in Data S1). The Gene Expression Omnibus and The Cancer Genome Atlas databases do not have relevant data and were therefore not included. The studies were required to have written the inclusion and exclusion criteria distinctly and clearly based on PICOS as follows: P, patients with BC; I, intensive DD chemotherapy; C, standard chemotherapy; O, survival rate and adverse effects; and S, randomized controlled trials (RCTs) and retrospective studies. Studies that met the aforementioned PICOS criteria were included in the present meta-analysis. After selection, the present study included RCTs and retrospective studies comparing intensive DD chemotherapy with standard chemotherapy in patients with BC, and patients with available information on pathological subtype and clinical stage were included. Studies with different durations of intensive DD chemotherapy and no available survival data were excluded. For DD chemotherapy, the experimental arm was designed to narrowly deliver agents over a shorter interval in the same cycle and dosage as the conventional schedule in the control arm. Survival data were synthesized and merged for analysis. No language restrictions were set, and reference lists from previous similar systematic reviews were also identified for potentially eligible studies.

Data extraction and quality assessment. A total of two reviewers (SD and ZTQ) independently performed the selection of the title and abstract and the evaluation of the full text of potentially eligible studies. Discrepancies between the two authors were resolved through discussion and by consultation with an experienced reviewer (ZYS). Eligible studies were analyzed for first author, publication year, study type, sample size (age range, before or after surgery, pre/postmenopausal status), tumor size (≤2.0, 2.1-5.0, ≥5.1) or tumor stage (T0-1/T2/T3-4), lymph node status (pN1/pN2-3) or (cN0-1/cN2-3), tumor grade (G1/G2/G3), estrogen/progesterone receptor (ER/PR) status, HER2 status and Ki-67 positivity (20%/>20%); DD type, agents and treatment cycle were extracted as baseline characteristics. For eligible RCTs, the Cochrane tool for assessing risk of bias (RoB 2.0) (14) was used to rate RCTs as follows: All low-risk domains were considered low-risk studies, one high-risk domain was considered a high-risk study and all other studies were considered unknown-risk studies. The quality of the eligible retrospective study was assessed using the Newcastle-Ottawa Scale score (15), with a score >4 considered acceptable.

To evaluate the effects of DD chemotherapy in patients with BC, overall survival (OS), disease-free survival (DFS), event-free survival (EFS), recurrence-free survival (RFS), pathologic complete response (pCR) and objective remission rate (ORR) were analyzed. BC subgroups of overall HR^+, HR^-, $Her2^+$, Her2 and triple-negative breast cancer (TNBC) were also evaluated. Luminal A and B classification could not be analyzed in subgroups due to limited data. Furthermore, the safety results related to DD chemotherapy included anemia, leukocytopenia, fatigue, diarrhea, nausea, vomiting and febrile neutropenia. The present study also used the Grading of Recommendations Assessment, Development, and Evaluation scales (16) to evaluate the quality of the outcomes from pairwise meta-analysis.

Statistical analysis. The present study performed pairwise meta-analyses for all direct comparisons with at least two different pathological types available and random effects network meta-analysis with a frequented approach to simultaneously combine direct and indirect evidence of all pathological types. For both pairwise meta-analyses and network meta-analysis, a random effects model to prevent inconsistencies was estimated. The present study assumed the variance of the heterogeneity model, which reported $P<0.05$ or $I^2>50\%$, indicating heterogeneity in the results (17).

For all results, the odds ratios (OR) and the hazard ratio (HR) with their corresponding 95% credible intervals (95% CI) were used to confirm significance of the meta-analysis results. Furthermore, a meta-analysis $P<0.05$ was used to determine whether a specific factor was the source of heterogeneity (18). Furthermore, Begg's and Egger's tests were performed to assess publication bias for available comparisons, and $P<0.05$ indicated the existence of publication bias.

The inconsistency between indirect sources of evidence was statistically assessed using a global (design-by-treatment inconsistency model) and a local method (back calculation) (19,20). The mean rank and relative treatment rankings were assessed for each intervention node according to the surface under the cumulative ranking curve (SUCRA) values and produced rankograms for the results of the OS and DFS analyses. The SUCRA score ranged from 0-100%, and a higher SUCRA indicated that patients with this pathological classification were more suitable for DD chemotherapy. Comparison-adjusted funnel plots were produced to explore the publication bias for network meta-analysis outcomes. All analyses were performed using StataSE version 15.1 (College Station, Texas 77845 USA).

Results

Study selection. A total of 449 publications were evaluated for eligibility after the removal of duplicates. After screening at the title and abstract level, 33 articles were left for full-text assessment. Furthermore, six records were removed based on a priori study selection criteria. A total of 27 studies (21-47) that included 27,580 patients were included in primary meta-analyses (Fig. 1). Of these, 25 studies were RCTs, including 12 that were phase III trials, and the remaining two were retrospective studies.

Study characteristics. The summarized characteristics of the studies are reported in Table I by pathological type and

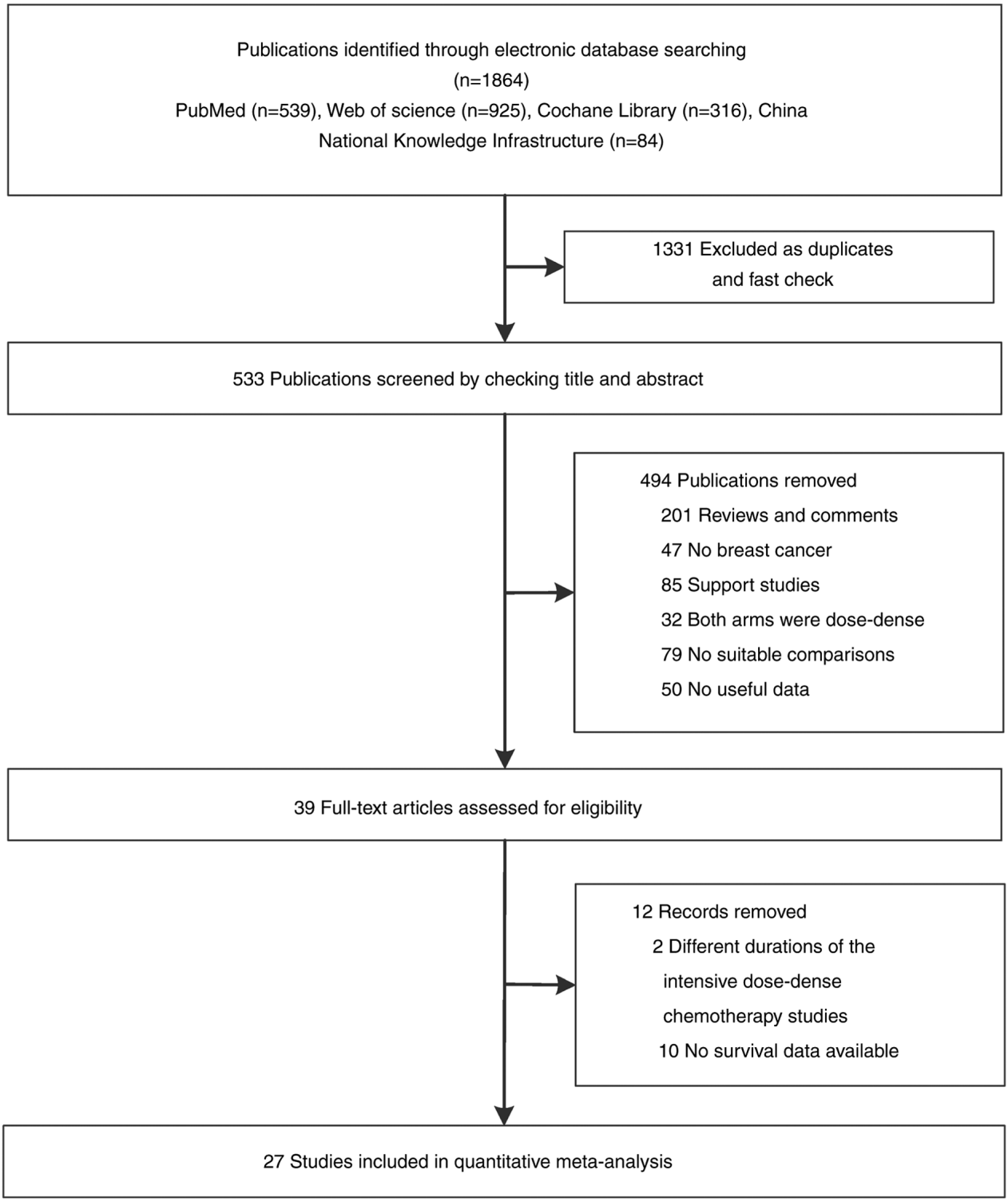

Figure 1. Flow chart of selection of quantitative studies in the meta-analysis. A total of 449 publications were evaluated for eligibility after the removal of duplicates. Ultimately, 27 studies that included 27,580 patients were included in the primary meta-analyses.

outcomes (see details in Table SI), with a sample size range of 43 to 3,264; of these, 17/43 included survival outcomes, such as the pathological subtype, which could provide data for the network meta-analysis (Table I). The baseline was balanced in terms of indicators before or after surgery, menopausal status, tumor size, lymph node status, ER/PR status, HER2 status and Ki-67 positivity (Table II). The worst tumor grade was determined in the DD chemotherapy group (Table II). Regarding quality assessment, all included studies achieved acceptable quality (Fig. S1; Table SII).

Evaluation of the effectiveness of DD chemotherapy from pairwise meta-analysis. All included studies included reporting of survival data for DD chemotherapy compared with standard chemotherapy. For OS, 13 studies provided HR data, and 30 of them provided OR data. Significant differences

Table I. Summarized characteristics of included studies.

Author, year	Pathological type	Outcome	Study type	Sample size (DD/S)	BC type	(Refs.)
Schneeweiss, 2022	HR^+, HR^-, $HER2^-$, $HER2^+$, TNBC	OS, DFS	RCT, phase III	470/475	Early	(21)
Gogas, 2012				551/535	All	(36)
Schneeweiss, 2019	HR^+, HR^-, $HER2^-$, $HER2^+$	OS	RCT, phase III	470/475	Early	(25)
Foukakis, 2016		OS, DFS, EFS, RFS	RCT, phase III	1001/1002	Early	(31)
Venturini, 2005		OS, EFS	RCT, phase III	604/610	Early	(44)
van Rossum, 2018	HR^+, $HER2^-$, TNBC	OS, RFS	RCT, phase III	332/332	All	(27)
Blondeaux, 2020	Overall, HR^+, HR^-	OS, DFS, EFS	RCT, phase III	604/610	Early	(23)
Del Mastro, 2015		OS, DFS	RCT, phase III	500/544; 502/545	Early	(32)
Untch, 2011				363/370	All	(39,40)
Untch, 2009				330/335	All	(43)
Lambertini, 2017		OS	RCT, phase III	267/261	All	(29)
Burnell, 2010		RFS	RCT	701/702	All	(41)
Moebus, 2010		OS, EFS	RCT, phase III	643/612	All	(42)
Liu, 2021	TNBC	OS, RFS	RCT, phase II	50/50	All	(22)
Bao, 2016		DFS	RCT	23/20	All	(30)
Jin, 2012				23/22	All	(37)
Zhou, 2015			Retrospective study	43/-	All	(33)
Möbus, 2018		OS	RCT, phase III	643/612	All	(26)
Cameron, 2017				1086/1116; 1084/1105	All	(28)
Therasse, 2003				224/224	Advanced	(47)
Swain, 2013		OS, DFS	RCT, phase III	1634/1630	Early	(34)
Zhu, 2013		DFS	RCT	24/27	Advanced	(35)
Arun, 2011			RCT, phase III	99/100	All	(38)
Baldini, 2003				73/77	Advanced	(45)
Citron, 2003			RCT	493/484; 495/501	All	(46)
He, 2020		pCR	Retrospective study	111/761	All	(24)

DFS, disease-free survival; EFS, event-free survival; OS, overall survival; RCT, randomized controlled trial; RFS, recurrence-free survival; DD, dose-dense; pCR, pathological complete response; HR, hormone receptor; TNBC, triple-negative breast cancer; BC, breast cancer.

Table II. Summary baseline indicators in the network meta-analysis.

Baseline indicator	OR (95% CI)	Heterogeneity (p, I^2)	Baseline information balance
Before or after surgery	1.040 (0.984, 1.099)	0.524, 0.0%	Yes
Menopausal status (Pre/post)	1.019 (0.952, 1.090)	0.048, 36.6%	Yes
Tumor size (≤5.0, ≥5.1) or (T0-T2/T3-4)	1.016 (0.935, 1.105)	0.095, 27.0%	Yes
Lymph node status (pN1/pN2-3) or (cN0-1/cN2-3)	0.902 (0.774, 1.052)	0.000, 88.0%[b]	Yes
Tumor grade (G1-G2/G3)	1.111 (1.017, 1.213)[a]	0.018, 45.1%	No
ER/PR status (positive/not)	1.045 (0.958,1.140)	0.000, 63.4%[b]	Yes
HER2 status (positive/not)	0.945 (0.820, 1.090)	0.000, 68.0%[b]	Yes
Ki-67 positive (≤20%/>20%)	1.160 (0.936, 1.436)	0.106, 47.5%	Yes

[a]P<0.05. [b]Substantial heterogeneity.

Table III. Subgroup meta-analysis of summary both HRa and OR outcomes from different pathological types on the efficacy of intensive DD chemotherapy for BC.

		Pairwise meta-analysis outcomes from HR value				Pairwise meta-analysis outcomes from OR value						
Outcome type	Pathological types	No. of studies	HRa (95% CI)	Heterogeneity (p, I^2)	Meta-regression P-value	No. subjects	OR (95% CI)	Heterogeneity (p, I^2)	Meta-regression P-value	Publication bias (P-values from Begg's test)	Publication bias (P-values from Egger's test)	Grade
Overall survival	Overall	13	0.82 (0.76,0.89)[a]	0.205, 23.6%	0.348	30 (22639)	0.92 (0.82,1.04)	0.000, 72.5%[b]	0.283	0.530	0.238	VERY LOW
	HR^+	13	0.75 (0.67,0.83)[a]	0.442, 0.30%		2 (959)	0.62 (0.18,2.16)	0.040, 76.2%[b]		1.000	-	LOW
	HR^-	11	0.77 (0.67,0.87)[a]	0.482, 0.0%		3 (788)	1.37 (0.93,2.02)	0.881, 0.0%		0.602	0.918	LOW
	$Her2^+$	3	0.82 (0.52,1.11)	0.689, 0.0%	0.678	3 (845)	1.57 (0.96,2.56)	0.333, 9.1%	0.656	0.602	0.530	LOW
	$Her2^-$	6	0.83 (0.55,1.11)	0.073, 50.4%[b]		5 (1,978)	1.11 (0.78,1.07)	0.157, 39.6%		0.327	0.439	VERY LOW
Disease-free survival	Overall	9	0.85 (0.79,0.91)[a]	0.474 0.0%	0.324	20	1.05 (0.90, 1.21)	0.000, 74.5%[b]	0.647	0.292	0.440	LOW
	HR^+	6	0.62 (0.30,0.95)[a]	0.003, 72.0%[b]		2	0.67 (0.34,1.35)	0.083, 66.8%[b]				VERY LOW
	HR^-	5	1.07 (0.71,1.44)	0.067, 54.5%[b]		1						
	$Her2^+$	2	0.62 (0.30,0.95)[a]	0.573, 0.0%	0.080[c]	2	0.80 (0.44,1.47)	0.137, 54.9%[b]	-			
	$Her2^-$	2	0.45 (0.21,0.70)[a]	0.903, 0.0%		2	0.69 (0.32,1.50)	0.059, 72.0%[b]				
	TNBC	3	1.18 (0.83,1.52)	0.412, 0.0%		4	1.58 (1.03, 2.43)[a]	0.600, 0.0%		0.117	0.176	VERY LOW
Event-free survival	Overall	4	0.77 (0.70,0.84)[a]	0.517, 0.0%	0.739	6	0.96 (0.72,1.27)	0.000, 83.4%[b]	0.771	1.000	0.962	LOW
	HR^+	4	1.01 (0.86,1.17)	0.905, 0.0%								
	HR^-	4	0.76 (0.65,0.88)[a]	0.909, 0.0%								
Recurrence-free survival	Overall	4	0.76 (0.61,0.91)[a]	0.193, 36.5%		3	0.99 (0.65,1.51)	0.004, 81.6%[b]		1.000	0.937	VERY LOW
Pathologic complete response						8 (4112)	1.19 (0.93, 1.52)	0.164, 33.1%		0.536	0.691	LOW
Objective remission rate						6 (2575)	1.48 (1.08, 2.04)[a]	0.126, 41.9%		0.707	0.789	LOW

[a]P<0.05. [b]Substantial heterogeneity. [c]Source of heterogeneity. BC, breast cancer; DD, dose-dense; HRa, hazard ratio; OR, odds ratio.

were found in the general group with low heterogeneity (HRa as in hazard ratios=0.82; 95% CI, 0.76 to 0.89; P=0.205; I^2=23.6%). Furthermore, the HR$^+$ and HR$^-$ subgroups also scored significant differences (0.75, 0.67 to 0.83; 0.77, 0.67 to 0.83). Furthermore, no significant difference in the OR results was found, with no sources of heterogeneity detected among meta-regressions that indicated low publication bias, ranging from very low to low grade (Table III).

For DFS, significant differences could also be found in the overall sample [0.85 (95% CI, 0.79 to 0.91)] and in the HR$^+$ [0.62 (95% CI, 0.30 to 0.95)], Her2$^+$ [0.62 (95% CI, 0.30 to 0.95)] and Her2$^-$ [0.45 (95% CI, 0.21, 0.70)] subgroups when considering outcomes and in the OR results of the TNBC subgroup [1.58 (95% CI, 1.03 to 2.43)], which had low heterogeneity in most subgroups and a small publication bias. Furthermore, meta-regression revealed that Her2$^+$ or HER1$^-$ status may have had a significant effect on the overall results (P=0.080). Significant differences in EFS could also be found in the overall sample [0.77 (95% CI, 0.70 to 0.84)] and for the HR$^-$ status group [0.76 (95% CI, 0.65, 0.88)] with no heterogeneity; likewise, there were significant differences in the overall RFS [0.76 (95% CI, 0.61 to 0.91)] for HRa outcomes and the ORR [1.48 (95% CI, 1.08 to 2.04)] with OR outcome (Table III).

Altogether, the present study revealed that DD chemotherapy successfully improved patient survival, especially with regard to OS and DFS. Subsequently, network meta-analysis was used to determine the most suitable pathological type of patients for DD chemotherapy. Furthermore, compared with OR, the HRa not only reflected the existence of events at the endpoint but also the time taken to reach the endpoint and the censored data. Therefore, the present study used HRa data for subsequent network meta-analysis.

Pathological subtypes of patients with BC suitable for DD chemotherapy derived from the network meta-analysis. The network graphs of direct comparisons between the 13 studies included in the network meta-analysis that provided OS data are shown in Fig. 2. Regarding the HRa outcome for OS, TNBC ranked the lowest with the lowest SUCRA score, and the second to last group was the overall patient sample. In terms of reduced survival risk, HR$^+$ was classified first, followed by Her2$^-$, Her2$^+$ and HR$^-$ BC subtypes, with no significant differences. Furthermore, DFS was classified as OS, and significance was found in subgroups of HR$^+$ [-0.85 (95% CI, -1.15 to -0.55)], Her2$^-$ [-0.94 (95% CI, -1.26 to -0.61)], Her2$^+$ [-0.73 (95% CI, -1.06 to -0.40)], HR$^-$ [-0.51 (95% CI, -0.91 to -0.11)] and the overall sample [-0.59 (95% CI, -0.89 to -0.29)] compared with TNBC. Significant differences were also identified when comparing the overall group in terms of HR$^+$ [-0.26 (95% CI, -0.47 to -0.05)] and Her2$^-$ [-0.35 (95% CI, -0.65 to -0.04)] status subgroups and when comparing the HR$^+$ and Her vs. HR$^-$ status subgroups (Fig. 3). In summary, DD chemotherapy may be more effective in patients with HR$^+$ and Her2$^-$ pathological subtypes.

Evaluation of the effectiveness of DD chemotherapy from pairwise meta-analysis. Grade 3 to 4 toxicity of DD chemotherapy compared with standard chemotherapy was reported in only 17 studies. DD chemotherapy did not increase the risk of serious leukocytopenia, fatigue, diarrhea, vomiting or febrile neutropenia. However, DD chemotherapy resulted in significant increases in the serious risk of anemia [3.024 (95% CI, 2.173 to 4.208)] and nausea [1.482 (1.096 to 2.004)], with low to substantial heterogeneity, low publication bias and low to moderate grade (Table IV).

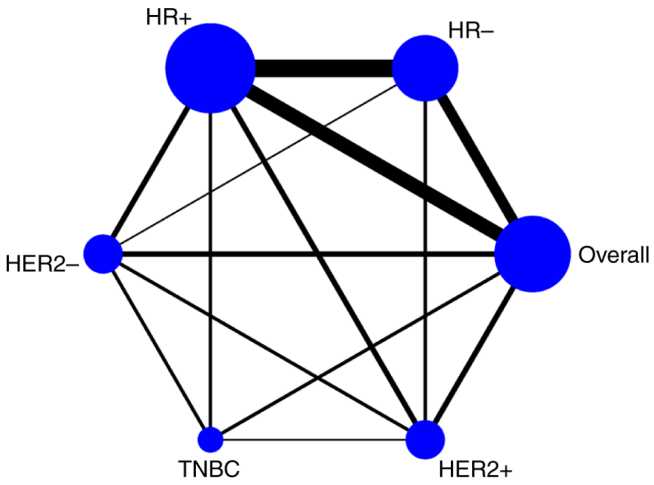

Figure 2. Network analysis of the efficacy in different pathological types of breast cancer of intensive dose-dense chemotherapy in terms of overall survival. Lines indicate direct comparisons that existed in this network meta-analysis, the width of the lines is proportional to the number of original studies with paired comparisons of pathological subtypes; size of each node is proportional to the number of patients. HR, hormone receptor; TNBC, triple-negative breast cancer.

Discussion

The present network meta-analysis systematically reviewed the efficacy and safety of DD chemotherapy in patients with BC and determined the most suitable pathological subtype that would benefit from DD chemotherapy. A total of 27 studies involving 27,580 patients were included and the baseline indicators were balanced, except for tumor grade. In addition, from the pairwise meta-analysis of efficacy outcomes of DD chemotherapy, significant differences were frequently found in the general, HR$^+$ and Her2$^-$ status subgroups in terms of HRa outcome. Moreover, the meta-regression revealed stratified patients with Her2 status and the heterogeneity source. Furthermore, the network meta-analysis indicated that patients with the HR$^+$, Her2$^-$ pathological BC subtype may be more responsive to DD chemotherapy. In addition, chemotherapy for DD can cause serious anemia and nausea. For patients with BC with HR$^+$ and Her2$^-$ pathology, chemotherapy for DD was recommended.

This network meta-analysis adhered to the PRISMA guidelines and was registered with the PROSPERO website, which means that the review was systematic and robust. The present study concluded that patients with BC with HR$^+$ and Her2$^-$ states were the pathological subtypes most suitable for intense DD chemotherapy. Similar conclusions were obtained by Puglisi *et al*, whereby DD adjuvant chemotherapy showed a consistent benefit in patients with early BC with HR$^+$/HER2$^-$ disease, although its effects varied according to the composite measure of the risk of recurrence (48). Lambertini *et al*

Table IV. Most frequent toxicities (grade III or higher) for patients treated with DD vs. standard treatment.

Outcome	No. of studies	OR (95% CI)	Heterogeneity (p, I^2)	Publication bias(P-values from Begg's test)	Publication bias (P-values from Egger's test)	Grade
Anemia	12	3.024 (2.173, 4.208)[a]	0.402, 4.3%	1.000	0.932	MODERATE
Leukocytopenia	10	1.360 (0.342, 5.407)	0.000, 98.8%[b]	0.592	0.785	LOW
Fatigue	8	1.223 (0.838, 1.786)	0.000,91.4%[b]	0.174	0.279	LOW
Diarrhea	15	1.227 (0.779, 1.934)	0.000, 78.9%[b]	0.621	0.993	LOW
Nausea	14	1.482 (1.096, 2.004)[a]	0.000, 77.6%[b]	0.228	0.951	LOW
Vomiting	17	1.273 (0.940, 1.722)	0.000, 74.5%[b]	0.773	0.573	LOW
Febrile neutropenia	11	0.815 (0.430, 1.544)	0.000, 96.2%[b]	0.876	0.639	LOW

[a]P<0.05. [b]Substantial heterogeneity.

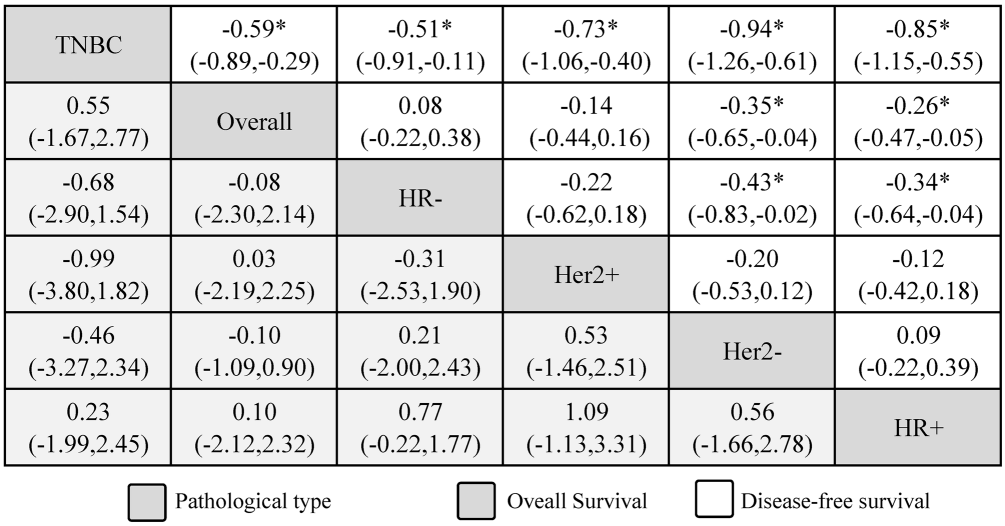

Figure 3. League tables of the efficacy in different pathological types of breast cancer of intensive dose-dense chemotherapy in terms of overall survival and disease-free survival. Comparisons between treatment agents should be read from left to right, and the estimates in the outcome cells are common between the column-defining treatment and the row-defining treatment. For the efficacy of the effect size model, an HRa <0 favors the column-defining treatment. *P<0.05.

concluded that DD chemotherapy is associated with a significant improvement in survival in patients with high-risk breast cancer. Its benefit is smaller in patients with $HER2^+$ disease who received adjuvant trastuzumab (6). In terms of safety outcomes, information regarding treatment with pertuzumab, trastuzumab and common anthracycline-containing regimens for the neoadjuvant treatment of early breast cancer resulted in cardiac and general safety profiles and pCR rates that were consistent with those from previous studies of pertuzumab (49). These studies support the present results and suggest that the safety of DD chemotherapy is acceptable.

Currently, standard chemotherapy based on anthracycline and taxane is still recommended for patients with $HER2^-/HR^+$ BC with a 21-day cycle. The present study recommended a 14-day cycle of chemotherapy without changing chemotherapy agents to achieve an improved patient benefit and acceptable safety. The mechanism of DD chemotherapy is more effective, as the DD regimen was less toxic to the immune system, presented reduced immunosuppression by the tumor microenvironment, and triggered macrophage recruitment and tumor-specific $CD8^+$ T-cell responses to tumors as determined by IL-2 and IFN-γ secretion (50). Furthermore, other mechanisms of action may also be involved, such as induction of apoptosis or inhibition of angiogenesis (51). Furthermore, DD chemotherapy may contribute to overcoming drug resistance, giving a high response rate, although durable remissions were achieved in few patients (52). These studies indicate that it is important to investigate non-traditional chemotherapy interval options for the treatment of BC.

There are also several limitations among the studies included in the meta-analysis. First, the baseline was not balanced as an indicator of tumor grade, which may have influenced the overall outcome. Second, the present study found that significant differences in OS and DFS data often appeared in HRa but not in OR data because HRa data were more accurate. Third, the present study did not perform a subgroup analysis based on the classification of chemotherapeutic agents or on the clinical stage because the included studies did not provide enough HRa data. Fourth, the sample size of the network meta-analysis may not have been large enough to show the

final conclusion. In the future, high-quality studies with larger sample sizes should be conducted in an effort to clearly report agents and clinical stages, thereby allowing network meta-analysis determination of the most suitable chemotherapeutic agents and clinical stage of patients to benefit from intensive DD chemotherapy. Finally, the present study found that repeated data were reported; for example, some data were included in both the HR^+ and $Her2^-$ groups, which may have also influenced the overall results. In conclusion, patients with HR^+ and $Her2^-$ BC are the most suitable pathological subtype to benefit from intense DD chemotherapy with an acceptable safety profile.

The findings of the present network meta-analysis represent studies with the best evidence base currently available and provide a guide on the choice of intense DD chemotherapy or standard chemotherapy regimens for patients. From a clinical standpoint, it is important to also consider the most suitable chemotherapy interval for different pathological subtypes in patients with BC, and it is hoped that these results will improve informed and shared decision-making processes for patients and clinicians. The present study hypothesized that intensive DD chemotherapy was most appropriate for patients with the luminal A type. Future studies should focus on the specific characteristics of patients to provide a personalized prediction of comparative effectiveness and safety with respect to the applicability of DD chemotherapy.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

DS, TQZ, and YSZ contributed to the study conception and design. Data collection and analysis were performed by DS, TQZ, HMH, XYS,YL and XYW. The first draft of the manuscript was written by DS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. DS and YSZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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