Efficacy of vinorelbine-based neoadjuvant chemotherapy in breast cancer: A systematic review and meta-analysis of randomized controlled trials

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Abstract. The present study aimed to compare the effects of vinorelbine-based neoadjuvant chemotherapy and vinorelbine-free regimens. A meta-analysis of all the relevant randomized controlled trials was performed to investigate the improvement in pathological complete response (pCR), overall response rate (ORR) and breast-conserving surgery (BCS). The PubMed and Embase databases were searched for relevant studies reporting randomized controlled trials comparing vinorelbine-based neoadjuvant chemotherapy with vinorelbine-free regimens until July 2013. Risk ratios/odds ratio and 95% confidence intervals (CIs) were used to estimate the association between vinorelbine in neoadjuvant chemotherapy and various efficacy outcomes. Fixed- or random-effect models were adopted to pool the data. Five eligible studies with a total of 1,495 patients were included in the meta-analysis. Compared to vinorelbine-free chemotherapy, vinorelbine-based regimens demonstrated no significant improvement in clinical outcomes including: pCR [relative risk (RR)=1.016; 95% CI, 0.738-1.399; P=0.922], ORR (RR=1.048; 95% CI, 0.969-1.133; P=0.239) and BCS (RR=1.764; 95% CI, 0.734-4.239; P=0.205). However, vinorelbine-based regimens were associated with a lower incidence of grade 3-4 alopecia (OR, 0.617; 95% CI, 0.448-0.848; P=0.003). In a hierarchical analysis for patients who received neoadjuvant chemotherapy, the proportion of subjects achieving pCR was significantly increased when HER2-amplified (RR=2.31; 95% CI, 1.20-4.43; P=0.01) and hormone receptor negative (RR=0.488; 95% CI, 0.263-0.908; P=0.023). The present review confirms that neoadjuvant chemotherapy vinorelbine-based regimens are unlikely to emerge as superior to pCR, ORR and BCS. Hierarchical analysis indicated that the HER2-amplified and hormone receptor-negative patients were significantly associated with a pathological response rate.

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Introduction

Neoadjuvant chemotherapy has emerged as the standard of care in the treatment of inoperable and operable locally advanced breast cancer. Neoadjuvant chemotherapy was used to afford tumor shrinkage and render tumors treatable for inoperable and locally advanced disease (1,2). Compared to patients with operable primary breast cancer, neoadjuvant chemotherapy can downstage the tumor so that breast-conserving surgery (BCS) becomes an alternative to mastectomy (2). Another benefit of neoadjuvant therapy is the unique opportunity for the evaluation of treatment response with pathological complete response (pCR) acting as a surrogate marker of survival. This allows a more rapid assessment of the efficacy of novel chemotherapeutic agents, also enabling early cessation of ineffective treatments and providing an opportunity to individualise patient treatment at an early stage. Despite the proven benefits of neoadjuvant treatment, no neoadjuvant chemotherapy regimens were recommended as the treatment of first choice. Anthracycline- or taxane-based neoadjuvant chemotherapy regimens are used widely, and other agents have been explored in clinical studies.

Vinorelbine is a semi-synthetic third generation vinca alkaloid with a broad spectrum of antitumor activity. Vinorelbine acts on the dynamic equilibrium of tubulin in the microtubulin apparatus of the cell. It inhibits tubulin polymerisation and binds preferentially to mitotic microtubules and blocks mitosis at G_2-M, causing cell death in interphase or at the following mitosis (3,4). The Breast Cancer Guidelines Committee of the National Comprehensive Cancer Network (NCCN) recommend vinorelbine as one of the first choices for patients with recurrent or metastatic breast cancer, but there are also other clinical studies exploring neoadjuvant treatment (5-8). Vinorelbine-based regimens were as effective and well-tolerated as vinorelbine-free regimens for breast cancer patients, and called for a neoadjuvant chemotherapy regimen

as an option for primary breast cancer (5). To more clearly understand vinorelbine-based regimens in neoadjuvant treatment for breast cancer patients, a meta-analysis was performed of the randomized controlled trials comparing neoadjuvant therapies with and without the drug for patients with breast cancer.

Materials and methods

Publication search strategy. PubMed and Embase were searched until July 2013 for randomized controlled trials regarding vinorelbine-based neoadjuvant chemotherapy for breast cancer. No language restrictions were used. The following search terms were used: 'Vinorelbine', 'neoadjuvant', 'preoperative', 'breast neoplasm' and 'breast cancer'. Manual searches were performed by reviewing the reference lists of retrieved studies, textbooks and review studies to identify additional potentially eligible studies.

Inclusion criteria. To be considered eligible for inclusion in the meta-analysis, the study criteria had to include: i) Patient diagnosis of breast cancer without metastasis; ii) being a controlled trial; iii) using vinorelbine in the neoadjuvant setting to treat breast cancer; and iv) reporting relative risk (RR) with a 95% confidence interval (CI); if not, the reported data of pCR, overall response rate (ORR) or BCS outcomes were sufficient to calculate them.

Data extraction. Two investigators (Hui Gao and Qiuyun Li) independently extracted information from the included studies. Disagreement was resolved by discussion between the two investigators. When multiple studies covering the same trial were retrieved, or when studies had overlapping study publications, only the largest number of participants with the most recent publication was included. The following data were extracted: First author's family name, year of publication, country of origin, regimens, number of cases and doses of regimens. Study quality was assessed using the Jadad score. Two investigators independently evaluated all the included trials based on an appropriate randomization method (0-2), an appropriate blinding method (0-2) and the study withdrawals and dropouts (0-1). Trials were considered to be of low quality if they reported none of the items, medium quality if they reported on <3 and of high quality if they reported on 3-5.

Statistical methods. All the statistical tests were performed using Stata/SE12.0 software (version 12.0; Stata Corp., College Station, TX, USA). The strength of association between the vinorelbine-based and vinorelbine-free regimens was assessed by calculating RR with 95% CIs based on the numbers in the controls. To test for heterogeneity in the included studies and analyze the statistical heterogeneity using the χ^2 test, $P \leq 0.10$ was considered to indicate a statistically significant difference. When heterogeneity did not exist between the results, I^2 heterogeneity quantitative analysis was used and the significance level was set at 50%, so $I^2 > 50\%$ indicated heterogeneity in the results. A random-effects model was used to pool the analysis when there was a genuine difference in the result. By contrast, if the difference in the studies was due to chance, then a fixed-effects model was used for meta-analysis.

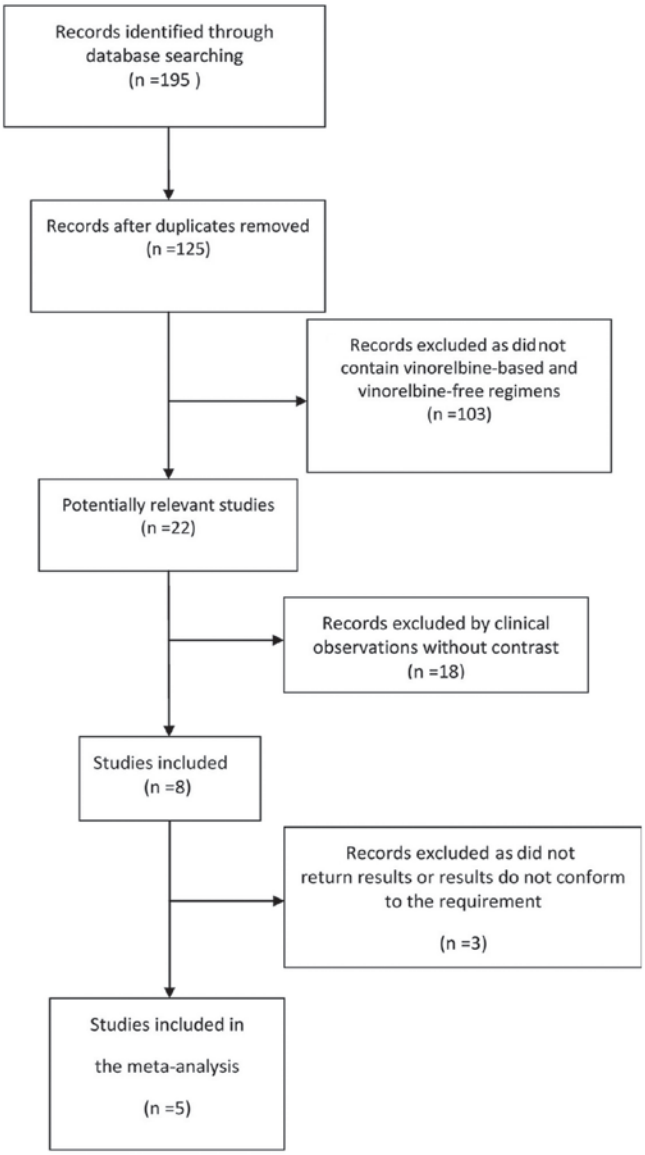

Figure 1. Flow chart of study selection.

Results

Patient characteristics. Five eligible studies (9-13) were identified with a total of 1,492 patients with early or operable breast cancer without distant metastasis according to the inclusion criteria (Fig. 1). In total, 675 patients were assigned to chemotherapy combined with vinorelbine and 817 to chemotherapy alone. The characteristics of the included trials are summarized in Table I. The median follow-up ranged between 2.2 and 5.1 years.

Krop *et al* (11) reported on a group receiving vinorelbine plus trastuzumab as neoadjuvant therapy and another receiving a standard combination of trastuzumab, docetaxel plus carboplatin. This study was only available as an abstract, while the full text was available for the remaining four studies. In the study by von Minckwitz *et al* (9), prior data for the group with complete or partial remission to 2 cycles TAC (docetaxel, doxorubicin and cyclophosphamide) followed by 4 or 6 cycles of TAC were excluded based on the inclusion criteria. All the studies included in the meta-analysis were

Table I. Characteristics of studies.

First author (year)	No. of patients	Agents and doses	Country	End-point	Jadad score	(Refs.)
Krop (2010)	41	N 25 mg/m^2 qwk + H 2 mg/kg qwk	America	pCR, ORR, BCS	2	(11)
	39	T 75 mg/m^2 q3wk + C^1 AUC 6 q3wk + H 2 mg/kg qwk				
Minckwitz (2011)	321	T 75 mg/m^2 + A 50 mg/m^2 + C 500 mg/m^2 on day 1	German	pCR, ORR, BCS	3	(9)
	301	N 25 mg/m^2 on days 1 and 8 + X 1,000 mg/m^2 twice a day on days 1-14				
Ferrero (1997)	68	A 40 mg/m^2 day 1+ V^1 1.4 mg/m^2 day 2 + C 300 mg/m^2 days 3-5 + F 500 mg/m^2 days 3-5	France	pCR, ORR, BCS	2	(13)
	47	A 40 mg/m^2 day 1 + V^2 3 mg/m^2 day 2 + C 300 mg/m^2 days 3-5 + F 500 mg/m^2 days 3-5				
	77	A 30 mg/m^2 day 1+ V^3 1.4 mg/m^2 day 2 + C 100 mg/m^2 days 1-14 + F 500 mg/m^2 days 1 and 8				
	46	A 50 mg/m^2 day 1 + N 25 mg/m^2 days 1 and 8				
Chua (2005)	238	N 25 mg/m^2 on days 1 and 8 + E 60 mg/m^2 on day 1	UK	pCR, ORR, BCS	2	(12)
	210	A 60 mg/m^2 + C 600 mg/m^2 day 1				
Gwak (2011)	53	A 50 mg/m^2 + D 75 mg/m^2	Korea	pCR, ORR, BCS	2	(10)
	49	A 50 mg/m^2 + N 25 mg/m^2				

N, vinorelbine; H, herceptin; T, docetaxel; C^1, carboplatin; A, doxorubicin; C, cyclophosphamide; X, capecitabine; V^1, vincristine; V^2, vindesine; V^3, vinblastine; E, epirubicin; D, docetaxel; pCR, pathological complete response; ORR, overall response rate; BCS, breast-conserving surgery; qwk, every week; q3wk, every 3 weeks.

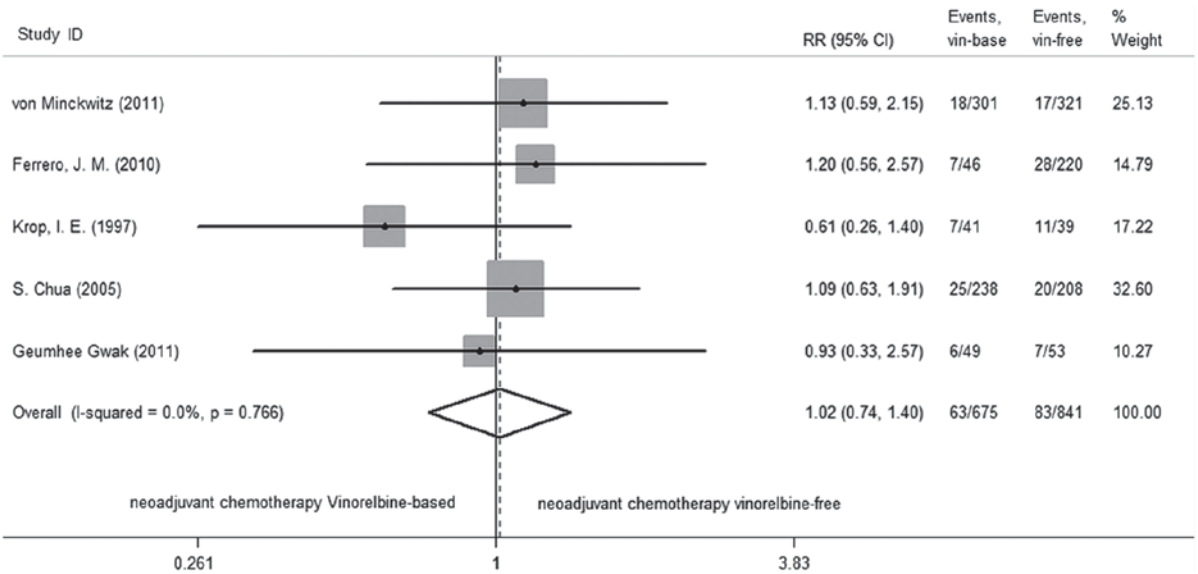

Figure 2. Fixed-effect model of the odds ratio (95% CI) of pCR associated with vinorelbine (vin)-based regimens in relation to neoadjuvant chemotherapy. pCR, pathological complete response; RR, relative risk; CI, confidence interval.

well-organized and had balanced populations. The main endpoint of all the five studies was pCR, and the second endpoint was ORR, BCS and various toxicities of the two arms.

First endpoint. Vinorelbine-based neoadjuvant chemotherapy was not associated with a significant improvement in pCR compared to vinorelbine-free regimens (RR=1.016; 95% CI, 0.738-1.399; P=0.922), There was no significant heterogeneity among studies (P=0.766, I^2=0.0%; Fig. 2).

Second endpoint. The next goal was the ORR in studies, following the generation of a fixed-effects model. There was no change in ORR (RR=1.048; 95% CI, 0.969-1.133; P=0.239) with vinorelbine-based regimens compared to vinorelbine-free regimens, and the test of heterogeneity did not exist in the studies (P=0.161, I^2=39.1%; Fig. 3).

There were three studies (9,10,13) that reported breast-conserving surgery for 415 patients and showed that the difference in the BCS was not statistically significant (RR=1.764; 95% CI, 0.734-4.239; P=0.205) between

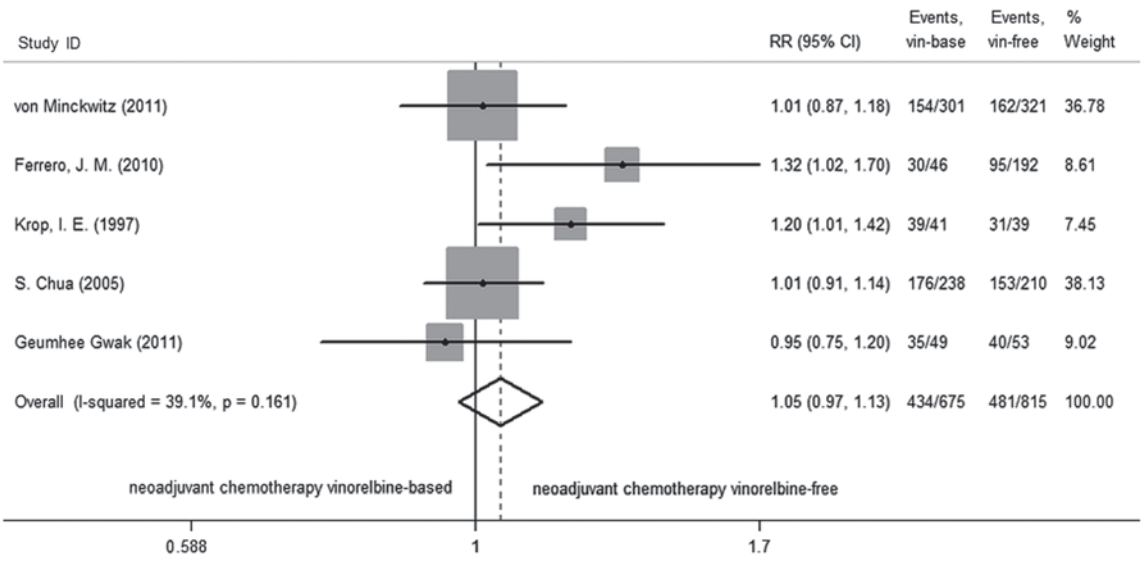

Figure 3. Fixed-effect model of the odds ratio (95% CI) of ORR associated with vinorelbine (vin)-based regimens in association with neoadjuvant chemotherapy. ORR, overall response rate; RR, relative risk; CI, confidence interval.

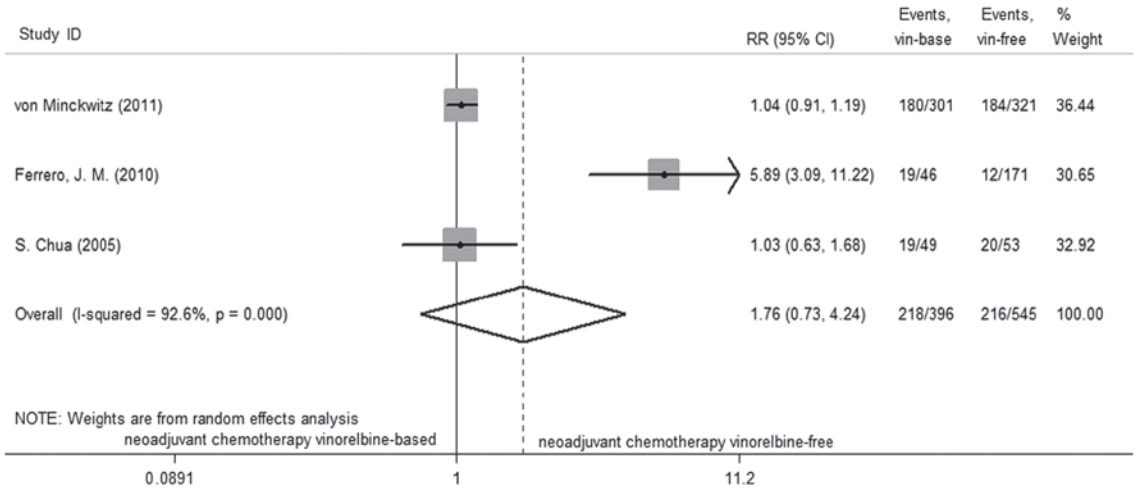

Figure 4. Random-effect model of the odds ratio (95% CI) of BCS associated with vinorelbine (vin)-based regimens in association with neoadjuvant chemotherapy. BCS, breast-conserving surgery; RR, relative risk; CI, confidence interval.

vinorelbine-based and vinorelbine-free regimens with regards to neoadjuvant therapy. The test for heterogeneity was statistically significant (P=0.000, I^2=92.6%). Therefore, an exploratory sensitivity analysis was performed to explore the source of the heterogeneity. Sensitivity analysis indicated that the outcome was not robust until the study by Ferrero *et al* (13) was excluded, and the heterogeneity could be mainly due to this study. The heterogeneity disappeared following the removal of this study, and the result also indicated that the difference in the BCS between the vinorelbine-based and vinorelbine-free regimens was not statistically significant (RR=1.042; 95% CI, 0.917-1.148; P=0.526), and the test of heterogeneity did not exist in studies (P=0.953, I^2=0.0%; Fig. 4).

Two studies (9,10) reported the postoperative outcomes in detail, as a hierarchical analysis, the rate of pCR of HER2 amplified was higher compared to HER2 non-amplified (RR=2.484; 95% CI, 1.296-4.760; P=0.006; Fig. 5) in neoadjuvant chemotherapy, and the test of heterogeneity did not exist (P=0.831, I^2=0.0%). The hormone receptor status was associated with the rate of pCR in neoadjuvant chemotherapy. The rate of pCR of hormone receptor-negative was significant different compared to hormone receptor-positive (RR=0.488; 95% CI, 0.263-0.908, P=0.023; Fig. 6), and the heterogeneity was not statistically significant (P=0.170, I^2=46.9%).

Toxicity. Table II presents the summary estimates of the vinorelbine-based and vinorelbine-free neoadjuvant chemotherapy regimen toxicity. The results show that treatment with vinorelbine-based regimens is associated with a lower incidence of grade 3-4 (National Cancer Institute Common Teminology Criteria for Adverse Events grades 3-4) alopecia (OR, 0.617; 95% CI, 0.448-0.848; P=0.003). Heterogeneity among the studies in the analysis was not significant regarding alopecia (P=0.378, I^2=0.0%). Neutropenia (OR, 0.436; 95% CI, 0.185-1.145; P=0.058), leukopenia (OR, 0.477; 95% CI, 0.190-1.196; P=0.114) and mucositis (OR, 0.680;

Table II. Summary estimate of the toxicity of neoadjuvant chemotherapy regimens vinorelbine-based and vinorelbine-free.

			Heterogeneity			Effect size		
Adverse events	No. of studies	No. of patients	P-value	I^2 (%)	Statistical model	OR	95% CI	P-value
Mucositis	3	1,172	0.342	6.9	Fixed-effect model	0.680	0.390-1.185	0.173
Alopecia	2	1,070	0.378	0.0	Fixed-effect model	0.617	0.448-0.848	0.003
Leukopenia	2	1,070	0.001	90.5	Random-effect model	0.477	0.190-1.196	0.114
Neutropenia	3	1,172	0.000	92.0	Random-effect model	0.436	0.185-1.145	0.058

OR, odds ratio; CI, confidence interval.

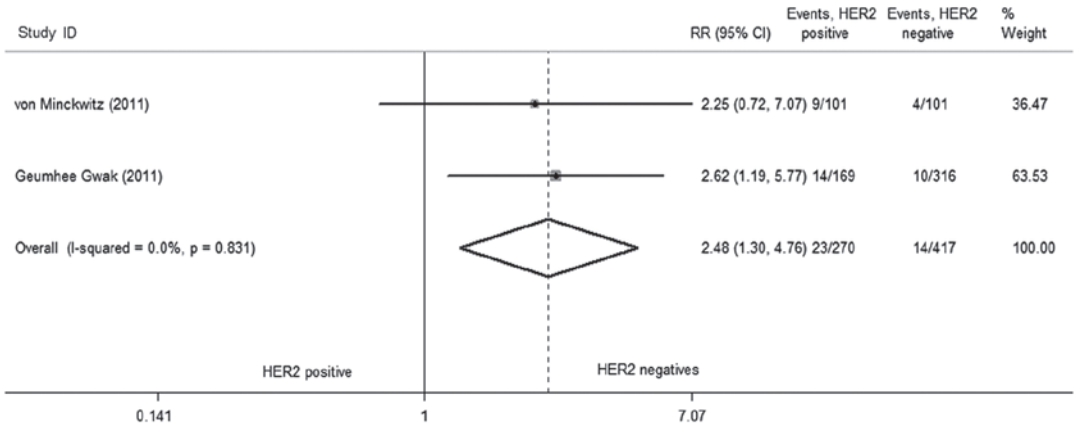

Figure 5. Fixed-effect model of the odds ratio (95% CI) of HER2 status associated with pathological complete response. RR, relative risk; CI, confidence interval.

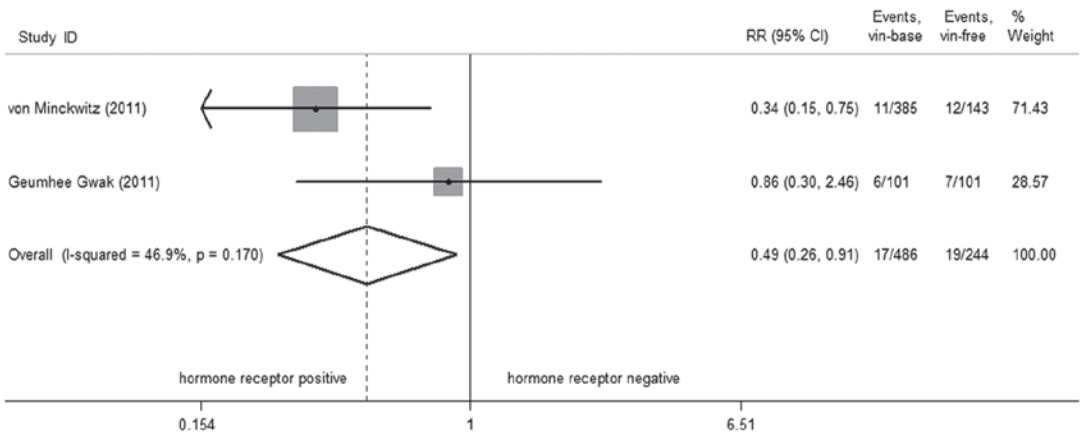

Figure 6. Fixed-effect model of the odds ratio (95% CI) of hormone receptor status associated with pathological complete response. RR, relative risk; CI, confidence interval.

95% CI, 0.390-1.185; P=0.173) showed no statistical significance between the two arms. Heterogeneity among the studies in these analyses was significant, possibly due to the use of various agents at different dosages and the use of different control arms.

Discussion

Neoadjuvant chemotherapy is one of the common therapies for antitumor treatment, and the most common agents used in patients with breast cancer were anthracyclines and taxane, although uncertainty remains for which to recommend as first choice. Vinorelbine was recommended for the treatment of recurrent breast cancer by the NCCN guidelines, and the exploration in neoadjuvant therapy has been in progress. Several trials reported that vinorelbine combined with others agents caused a certain effect (7,14-16). In order to reassess the data that are already present in the literature with the largest possible statistical power, we carried out what is, to the best of our knowledge, the first meta-analysis of the effects of including vinorelbine as part of neoadjuvant polychemotherapy in patients with breast cancer. The findings show no benefit

from neoadjuvant therapy in patients with vinorelbine-based compared to patients with vinorelbine-free regimens. pCR is the most powerful predictor of neoadjuvant chemotherapy (17,18). Patients who achieved a pCR following neoadjuvant chemotherapy have an improved prognosis compared to those who remain with residual disease, which shows improvements in DFS and OS (19,20). A higher pCR rate has become one of the indicators of neoadjuvant chemotherapy. Therefore, the first goal of the present meta-analysis was pCR assessment. From the five studies, we identified vinorelbine-based regimens without any advantage in pCR (21). However, this shows another problem, as comparing to the vinorelbine-free regimens, vinorelbine-based regimens show no weakness in pCR in comparison to other regimens in neoadjuvant chemotherapy.

Although the present meta-analysis did not demonstrate an advantage of adding vinorelbine to neoadjuvant therapy for breast cancer, certain notable results did emerge from the included studies. von Minckwitz *et al* (9) and Gwak *et al* (10) reported four molecular outcomes in detail following surgery. Patients with HER2-amplified or hormone receptor-negative may have an additional benefit from neoadjuvant therapy to achieve pCR, which suggests that patients with different HER2 or hormone receptor status have different sensitivity for neoadjuvant therapy, although there were poor prognostic factors (22). The similar association between molecularly and pCR has been reported previously. Yoo *et al* (23) reported that the triple-negative is more likely to obtain pCR when neoadjuvant chemotherapy is administered, but there are worse survival outcomes. Houssami *et al* (24) also obtained similar results; triple-negative or $HER2^{+}/HR^{-}$ subtypes achieve higher odds of pCR.

However, the present meta-analysis showed that the rate of BCS was not improved following neoadjuvant therapy. Certain strong heterogeneity was identified among the studies, and the reasons are list as followed. First, the decision of the surgeon to perform surgery was not only according to the result of neoadjuvant chemotherapy, but also considering other comprehensive situations. Second, the choice of surgery is strongly influenced by the willingness of the patient, the level of development of the country or region cognitive to breast cancer. Studies of different countries illustrate different BCS. Suen *et al* (25) reported that 21.9% of patients with early-stage breast cancer underwent BCS among 680 patients between January 2001 and December 2005 in Hong Kong. Clavarezza *et al* (26) reported that 34% of patients achieved breast-conserving surgery after four 3-weekly cycles of fluorouracil, epirubicin and cyclophosphamide followed by 12 cycles of weekly paclitaxel as neoadjuvant therapy in Italy. Further research and feasibility studies are required to demonstrate this.

The present analysis included five randomized controlled trials of varying quality and had the following limitations. First, despite the fact that no language restrictions were applied to the literature search, only one non-English language study was identified. It is possible that certain relevant clinical data published in other languages may have been overlooked. Second, one randomized controlled trial had no full text and another one had data pooled by the author, therefore, the heterogeneity is likely to increase. Finally, the characteristics of the included trials were varied in patients, time and dosage. The five trials did not use the double-blinding method. Future studies should attempt to minimize these possible sources of heterogeneity.

Despite the limitations of the present study, the results strongly demonstrate that vinorelbine-based neoadjuvant chemotherapy did not significantly improve pCR, ORR and BCS. HER2-amplified and hormone receptor-negative patients were significantly associated with the pathological response rate, but not the lymph node status and tumor size.

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