

Research Paper

Significantly higher pathologic complete response (pCR) after the concurrent use of trastuzumab and anthracycline-based neoadjuvant chemotherapy for HER2-positive breast cancer: Evidence from a meta-analysis of randomized controlled trials

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Received: 2018.01.02; Accepted: 2018.03.21; Published: 2018.08.06

Abstract

Objectives: To investigate the effect of the concurrent use of trastuzumab and anthracycline-based neoadjuvant chemotherapy (NAC) for HER2-positive breast cancer in terms of pCR and cardiotoxicity.

Methods: We systematically searched Pubmed, Embase, Cochrane and SinoMed databases from inception until 1 July 2017 for relevant articles of randomized controlled studies. After identified all relevant studies that reported the concurrent use of trastuzumab and anthracycline-based NAC for HER2-positive locally advanced breast cancer, five eligible randomized studies were extracted relevant data and assessed for design and quality, and the meta-analysis was conducted to evaluate the risk ratio (RR) of pCR and other interesting outcomes, such as left ventricular ejection fraction (LVEF) decrease more than 10%, responses, recurrence free survival (RFS) and overall survival (OS).

Results: A total of five randomized controlled studies were included in the meta-analysis, including 232 HER2-positive locally advanced breast cancer patients received the concurrent use of trastuzumab and anthracycline-based NAC. The results showed that the pCR rate was significantly higher in the group received the concurrent use of trastuzumab and anthracycline-based NAC (48%) than that in the non-concurrent use of trastuzumab and anthracycline-based NAC group (26%) (RR: 1.76, 95%CI: 1.37-2.26, $p < 0.0001$). Besides, higher rate of RFS (RR: 1.14, 95%CI: 1.03-1.26, $p = 0.009$) was observed in the concurrent use of trastuzumab and anthracycline-based NAC group. No significant differences in LVEF decreased more than 10% ($p = 0.50$) between both groups.

Conclusions: Our meta-analysis of randomized controlled studies showed that pCR rates are significantly higher in the concurrent use of trastuzumab and anthracycline-based NAC compared with the non-concurrent use of trastuzumab and anthracycline-based NAC for certain HER2-positive breast cancer, meanwhile without significant increase of the cardiotoxicity.

Key words: Breast cancer; Neoadjuvant chemotherapy; Pathologic complete response (pCR); Human epidermal growth factor receptor 2 (HER2); Meta-analysis

Introduction

Neoadjuvant chemotherapy (NAC) has become an essential and standard approach for the treatment of locally advanced breast cancer, which would cure distant micro-metastases, downstage tumors,

improve operability and make breast conservation surgery possible [1, 2]. The responses to the NAC in the breast cancer patients would partly predict the prognosis of the patients, so better responses to the NAC are more likely to obtain better outcomes. Meanwhile, different subtypes of breast cancer and different NAC regimens may predict different responses to preoperative chemotherapy [3].

According to the molecular subtyping of breast cancer, which based on the status of hormone receptors and human epidermal growth factor receptor 2 (HER2), 25%-30% breast cancer with overexpression or amplification of HER2, which is defined as HER2-positive breast cancer and indicated active proliferation of tumorigenesis [4, 5]. HER2-positive breast cancer was reported to be resistant to certain chemotherapy agents, such as cyclophosphamide, methotrexate and fluorouracil [6]. However, HER2-positive tumors were reported to be high sensitive to anthracyclines- or taxanes-containing chemotherapy [7]. Anthracycline-based regimen is one of the most frequent treatments in NAC of breast cancer, and anthracycline-based regimens are superior to non-anthracycline-based regimens for HER2-positive tumors [7]. Besides, survival benefit of HER2-positive breast cancer patients has dramatically improved since trastuzumab, the HER2-targeted drug, has become available in the treatment of HER2-positive breast cancer [8, 9]. In previous randomized studies, NAC of anthracycline-based regimen concurrent with trastuzumab showed a favorable efficacy in local advanced HER2-positive breast cancer, which had not caused significant increase of cardiotoxicity [10-14]. However, in a randomized study, cardiac dysfunction was occurred in 27% of the HER2-positive metastatic breast cancer patients who received trastuzumab and anthracycline-based combination therapy [5]. Although no significant increase in survival benefit after NAC, several studies have shown that significant improvement of outcomes were obtained when patients achieved pathologic complete response (pCR) [15-17]. It is emphasized that the aim of NAC for locally advanced breast cancer is not only to downstage tumors and improve operability, but also to achieve pCR. Therefore, it is important to optimize the NAC regimen for locally advanced breast cancer. However, the pCR and cardiotoxicity of the concurrent use of trastuzumab and anthracycline-based NAC is controversial [18].

Here, we perform a meta-analysis of randomized controlled studies to compare the pCR rate of concurrent versus non-concurrent use of trastuzumab and anthracycline-based NAC in HER2-positive locally advanced breast cancer.

Materials and Methods

The systematic review and meta-analysis was conducted in accordance with PRISMA guidelines [19]. This study was conducted in accordance with an established protocol and prospectively registered in PROSPERO (International prospective register of systematic reviews) [20], and the registration information is available on <https://www.crd.york.ac.uk/PROSPERO/> (Registration number: CRD42017071432).

Eligibility criteria

We considered randomized studies that had studied the concurrent use of trastuzumab and anthracycline-based NAC (experiment group) with a control group (Non-concurrent use of trastuzumab and anthracycline-based NAC, such as anthracycline-based NAC alone or trastuzumab plus non-anthracycline-based NAC) for HER2-positive breast cancer. Randomized controlled studies with the concurrent use of trastuzumab and anthracycline-based NAC were eligible for meta-analysis if they reported the data of pCR. Studies were ineligible: (1) reviews, case reports and non-randomized studies. (2) No experiment or control group or unable to extract relevant data of interesting outcomes. (3) Cases with metastasis or coexist of other malignancies. (4) Cases were not HER2-positive breast cancer patients. HER2-positive breast cancer is defined as HER2 immunohistochemistry score of 3+ or fluorescence in situ hybridization (FISH) indicates HER2 gene amplification.

Search strategy

We searched Pubmed, Embase, Cochrane and SinoMed (Chinese Biomedical Database) databases from inception until 1 July 2017 for relevant articles in any language. The references were searched by a combination of medical subject heading terms and/or free text words, such as "breast neoplasm", "breast cancer", "breast carcinoma", "neoadjuvant", "preoperative", "anthracycline", "doxorubicin", "epirubicin", "herceptin" and "trastuzumab" (S1 Appendix Data). Two investigators (JSW and KZ) independently performed the references search, a third investigator (YTW) was consulted when disagreement arose.

Outcome measures

The primary outcomes were the rates and the risk ratio (RR) of pCR compared the concurrent with non-concurrent use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer, and the secondary outcomes was the RR of left ventricular ejection fraction (LVEF) decrease more

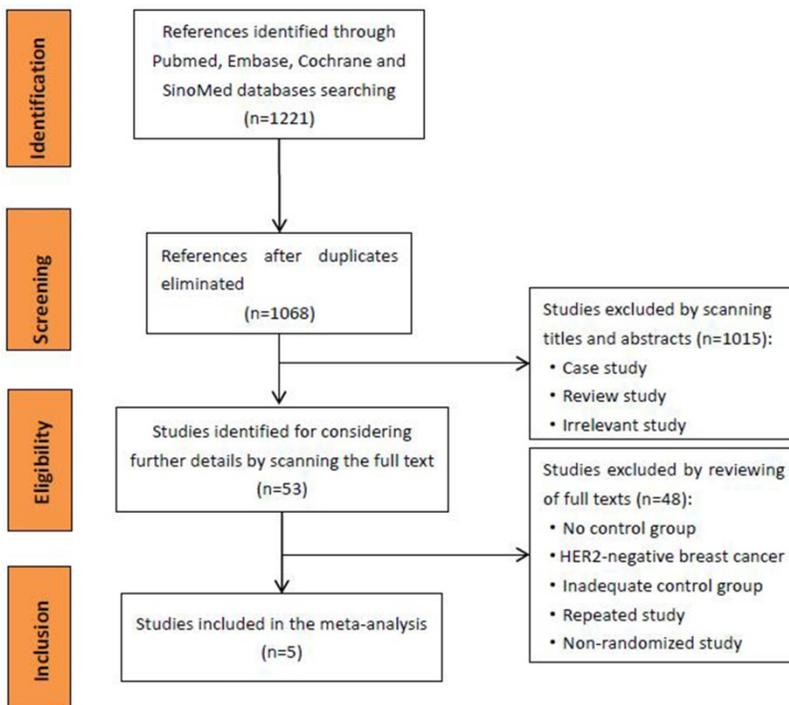


Figure 1. Preferences selection flow diagram

than 10%, cardiac failure (CF), responses (complete response and partial response), breast conversion surgery (BCS), recurrence free survival (RFS) and overall survival (OS).

Study selection

All 1221 references were identified after databases searched. After duplicates removed, two researchers independently assessed the eligible studies, titles and abstracts of articles were scanned. After that, we reviewed the full text of possible articles according to the inclusion/exclusion criteria. Finally, total 5 studies [10-14] were included in the meta-analysis (Fig 1).

Data extraction and quality assessment

Two researchers (ZX and BA) independently extracted information of the eligible studies using electronic tables. The following items were extracted from eligible articles: Basic information, including the year of study publication, country, study design, sample size, age, chemotherapy regimen, type of cancer, time of follow-up. Besides, data of outcomes information was collected.

The bias risk assessment was conducted according to the Cochrane Collaboration Risk of Bias Assessment Tool (<http://www.cochrane.org>). Two reviewers (JSW and KZ) independently evaluated the methodological quality, a third investigator (YTW) was consulted when disagreement arose between the prior reviewers. The assessment has seven parameters

of quality assessment for randomized controlled studies, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective bias and other biases. Each parameter has three categories of biases: low risk of bias, unclear risk of bias and high risk of bias. All studies were deemed to have a high risk of blinding of participants and personnel because it was difficult to make patients blinding in relevant trials. After evaluation, all studies were assessed to have appropriate quality of methodology.

Statistical analysis

We pooled the absolute rate of pCR in the experiment group and control group, and risk ratio (RR) with 95% confidence intervals (CI) of pCR compared the concurrent with non-concurrent use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer. The secondary outcomes were also pooled. The meta-analysis statistics was carried out using the Cochrane Collaboration's Review Manager Software (RevMan, version 5.3; Oxford, United Kingdom) and R software (version 3.3.2, R Foundation for Statistical Computing). Probability values were two-sided, and $P < 0.05$ was considered of statistical significance. Statistical heterogeneity was evaluated using the I-squared (I^2) and chi-squared (χ^2) tests. I^2 values of 25%, 50%, 75% indicated low, moderate and high level of heterogeneity, respectively. Data was not pooled if the I^2 was greater than 40%. A p value of < 0.1 for χ^2 was defined to indicate the presence of heterogeneity. Results were pooled using the maximum likelihood estimation, a random effect model was used for analysis if heterogeneity existed, and otherwise a fixed effect model was used. Besides, sensitivity analysis was performed by excluding the heterogeneity study or the study of the least sample size depending on the presence or absence of significant heterogeneity. Funnel plots and the Egger's test of funnel plot asymmetry were used to evaluate publication bias.

Results

Description of included studies

In total, we included 5 randomized controlled studies [10-14] in concordance with eligibility criteria

after ineligible studies were excluded from all the identified references (Fig 1), which including 232 [Median age: 48.5 (range: 21-71)] and 212 [Median age: 46.8 (range: 25-75)] HER2-positive breast cancer patients concurrent and non-concurrent use of trastuzumab and anthracycline-based NAC,

respectively. We summarized the baseline study characteristics in Table 1 and extracted data in S1 table. The 5 studies included two from America, two from China and one study was international multicenter study (six countries and 27 centers).

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

Study, Year	Country	Type of study	Total participants (EH/No EH)*	Median age (range)(years)	Chemotherapy regimen	Baseline left ventricular ejection fraction (LVEF)	Anthracycline	Type of cancer	Outcome measures	Median of follow-up (months)
Buzdar et al, 2005	USA	Prospective randomized trial	42(23/19)	EH:52(29-71) No EH:48(25-75)	Paclitaxel (225mg/m ²), FEC (fluorouracil 500mg/m ² , day 1,4; cyclophosphamide 500mg/m ² , day 1; epirubicin 75mg/m ² , day 1), trastuzumab (4mg/kg, day 1 of the first cycle, followed by 2mg/kg, weekly). Four cycles of paclitaxel followed by four cycles of FEC, cycles repeated every 3 weeks, with or without simultaneous trastuzumab.	Patients with a history of uncompensated congestive heart failure or a cardiac ejection fraction less than 45% were excluded.	Epirubicin	HER-2 positive and clinical stage II to IIIa.	pCR; CR; PR; RFS; Rate of breast conservation; Cardiac ejection fraction; Cardiac failure.	20
Buzdar et al, 2007	USA	Prospective randomized trial	41(22/19)	EH:51(21-70) No EH:48(25-75)	Four cycles of paclitaxel (225mg/m ² , every 3 weeks), followed by four cycles of FEC (fluorouracil 500mg/m ² , day 1,4; cyclophosphamide 500mg/m ² , day 1; epirubicin 75mg/m ² , day 1), trastuzumab (4mg/kg, day 1 of the first cycle, followed by 2mg/kg weekly). P-FEC/PH-FECH.	Patients with a history of uncompensated congestive heart failure or a cardiac ejection fraction less than 45% were excluded.	Epirubicin	HER-2 positive and clinical stage II to IIIa.	pCR; RFS; Cardiac ejection fraction; Cardiac failure.	36.1
Gianni et al, 2010	International multicenter study (six countries and 27 centers)	Prospective phase III randomized trial	235(117/118)	<50years EH:50p No EH:50p >50years EH:67p No EH:68p	Doxorubicin 60mg/m ² plus paclitaxel 150mg/m ² , every 3 weeks for three cycles, followed by paclitaxel 175mg/m ² administered every 3 weeks for four cycles. Cyclophosphamide 600mg/m ² and fluorouracil 600mg/m ² were then given on days 1 and 8 every 4 weeks for three cycles. Trastuzumab 8mg/kg loading dose, followed by 6mg/kg, every 3 or 4 weeks. TEH-FCH/TE-FC.	EH:63%(55-82) No EH:63%(55-89)	Doxorubicin	HER-2 positive locally advanced or inflammatory breast cancer.	pCR; RFS; OS; Cardiac ejection fraction.	38.4
Huang et al, 2015	China	Phase II randomized trial	87(41/46)	EH:47.5(30-63) No EH:48(29-65)	Paclitaxel (75mg/m ² , weekly), trastuzumab (4mg/kg loading dose followed by 2mg/kg), carboplatin (AUC=2, weekly), epirubicin (75mg/m ² , every 3 weeks). At least 4 cycles but no more than 6 cycles. PEH/PCH.	EH:67%(58-79) No EH:65%(56.5-83)	Epirubicin	HER-2 positive and clinical stage II to III.	pCR; CR; PR; NR Cardiac ejection fraction; Cardiac failure.	
Yu et al, 2016	China	Randomized controlled trial	58(29/29)	EH:45.2(35-62) No EH:44.1(33-59)	Epirubicin 40mg/m ² , docetaxel 60mg/m ² , trastuzumab 4mg/kg, every 3 weeks, 4 cycles. TEH/TE.	NR	Epirubicin	HER-2 positive and clinical stage II to III.	pCR; CR; PR; OS; RFS.	60

We evaluated the quality of the included studies using Cochrane Collaboration Risk of Bias Assessment Tool in S2 table. As a result, all of the included studies were of eligible quality, which indicated that all the included studies were reliable. Besides, we assessed the publication bias of the included studies using symmetrical funnel plot analysis and Egger's tests, and the result showed no significant publication bias was found. Meanwhile, we found no significant between-study heterogeneity ($I^2=0\%$), thus the fixed-effect model was used.

Pathologic complete response

Total five randomized studies, including 443 patients (232 in the experiment group and 212 in the control group), were analyzed for the pCR rate of HER2-positive breast cancer patients concurrent and

non-concurrent use of trastuzumab and anthracycline-based NAC. The absolute pCR rate was pooled to be 48% (95%CI: 0.42-0.54) in the concurrent use of trastuzumab and anthracycline-based NAC group and 26% (95%CI: 0.21-0.32) in the non-concurrent use of trastuzumab and anthracycline-based NAC group (Fig 2).

The pCR rate was significantly higher in the concurrent use of trastuzumab and anthracycline-based NAC compared to the group with non-concurrent use of trastuzumab and anthracycline-based NAC, corresponding RR was 1.76 (95%CI: 1.37-2.26, $p<0.0001$) (Fig 3). The pCR rate increased from 26% to 48%, absolute increase of 22%. $I^2<25\%$, p for heterogeneity was <0.05 , thus a fixed-effect model was used.

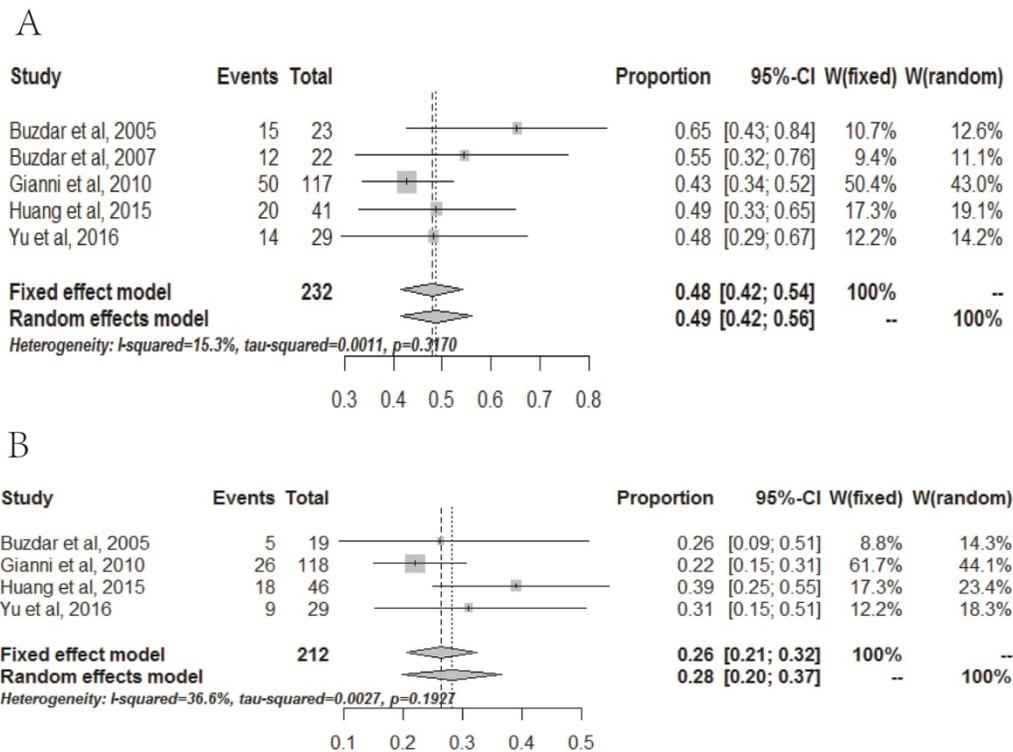


Figure 2. The pooled absolute rate of pCR for the concurrent (A) and non-concurrent (B) use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer

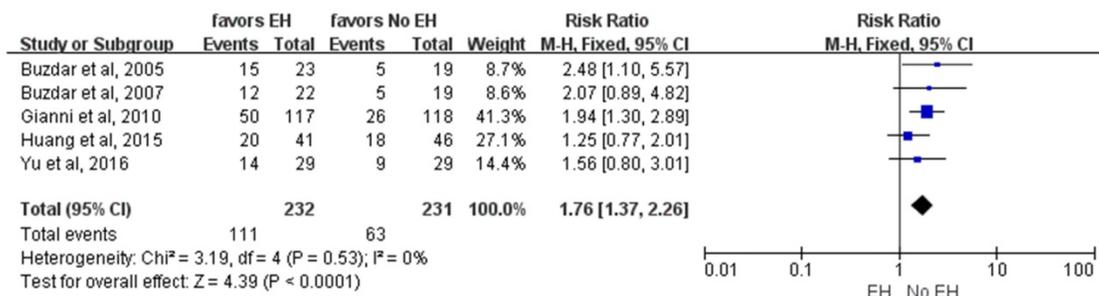


Figure 3. The RR of pCR for the comparison of the concurrent versus non-concurrent use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer. **EH:** the group of concurrent use of trastuzumab(H) and anthracycline(E)-based NAC for HER2-positive breast cancer. **No EH:** the group of non-concurrent use of trastuzumab(H) and anthracycline(E)-based NAC for HER2-positive breast cancer.

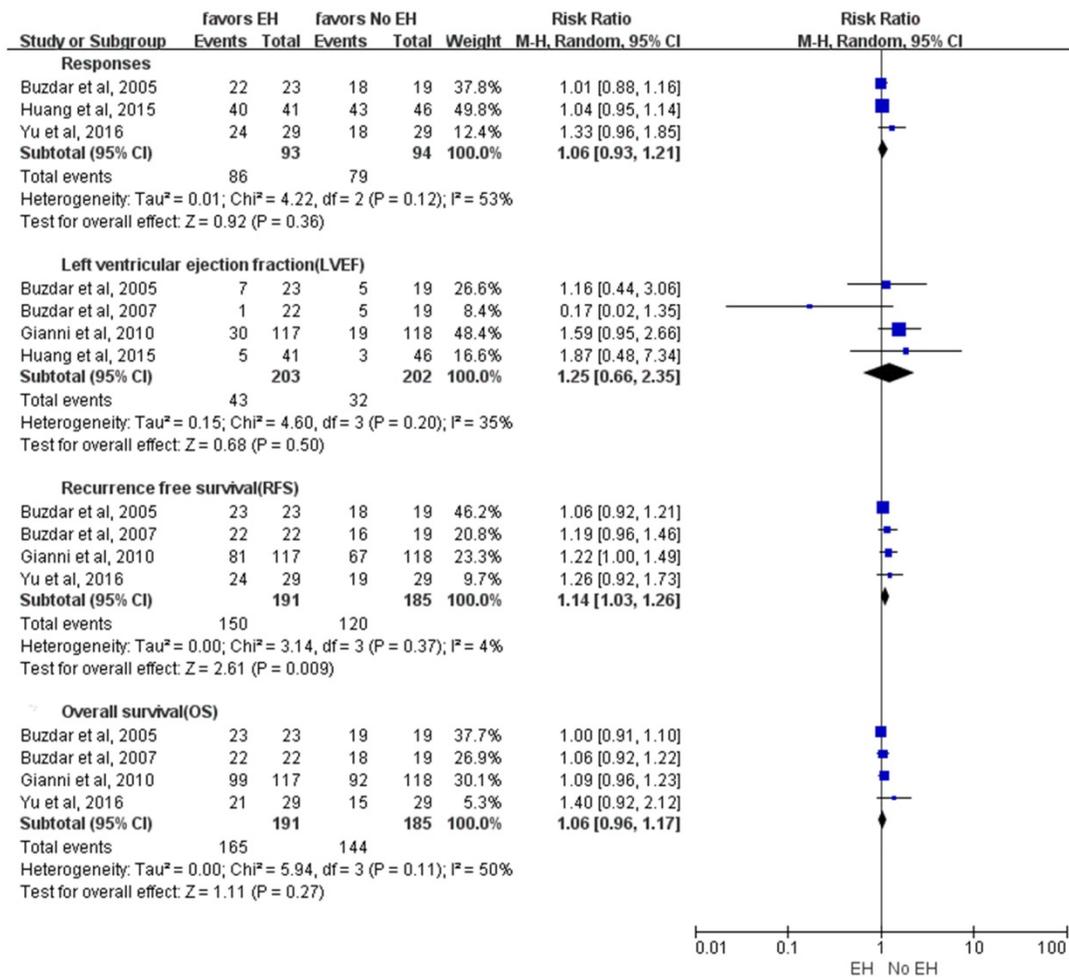


Figure 4. The RR of secondary outcomes for the comparison of the concurrent versus non-concurrent use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer. **EH:** the group of concurrent use of trastuzumab(H) and anthracycline(E)-based NAC for HER2-positive breast cancer. **No EH:** the group of non-concurrent use of trastuzumab(H) and anthracycline(E)-based NAC for HER2-positive breast cancer.

Secondary outcomes

Some secondary outcomes reported in the included studies were pooled. For the rate of responses, no significantly higher responses rate was observed in the concurrent use of trastuzumab and anthracycline-based NAC group (RR: 1.06, 95%CI: 0.93-1.21, p=0.36) (Fig 4). During the period of follow-up, the RFS and OS were reported in four studies. Compared with the non-concurrent use of trastuzumab and anthracycline-based NAC group, the concurrent used of trastuzumab and anthracycline-based NAC group had a better RFS (RR: 1.14, 95%CI: 1.03-1.26, p=0.009) (Fig 4), but the OS had no significant difference (RR: 1.06, 95%CI: 0.96-1.17, p=0.27) (Fig 4). Heterogeneity was observed, a random-effect model was used.

For the cardiotoxicity, four studies had reported the LVEF decrease more than 10% events. According to our pooled analysis, the LVEF decrease more than 10% events were not significant different in both groups (RR: 1.25, 95%CI: 0.66-2.35, p=0.50) (Fig 4).

Besides, only one study reported that two patients developed a reversible symptomatic cardiac failure in the concurrent use of trastuzumab and anthracycline-based NAC group [12]. For the BCS, as reported by Buzdar et al [10], BCS was performed in 10 (52.6%) and 13 (56.5%) patients in the concurrent and non-concurrent use of trastuzumab and anthracycline-based NAC groups, respectively.

Discussion

This meta-analysis of randomized controlled studies provides a comparison of the pCR and cardiotoxicity between the concurrent and non-concurrent use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer. Two previous meta-analyses had suggested that the concurrent use of trastuzumab and NAC for HER2-positive breast cancer would improve the pCR rate [21, 22]. However, previous studies did not conducted subgroup analysis for efficacy of the concurrent use of trastuzumab and anthracyclines, corresponding pCR rates and toxic effects were not

reported. Considering the cardiotoxicity of both trastuzumab and anthracyclines, the concurrent use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer patients should be more careful [23-25]. Several randomized studies [10-14] had evaluated the efficacy and toxic effects of the concurrent use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer, thus we performed this meta-analysis to make a further study.

Our study suggests that a higher rate of pCR were acquired in the concurrent use of trastuzumab and anthracycline-based NAC (48%) compared to the non-concurrent use of trastuzumab and anthracycline-based NAC (26%) for HER2-positive breast cancer. Besides, during the period of follow-up, the concurrent use of trastuzumab and anthracycline-based NAC had led to a better RFS rate, but the OS was not significantly different. Similar results have been seen in previous studies, the concurrent use of trastuzumab and anthracycline-based NAC is superior to the non-concurrent use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer in terms of pCR. NAC for breast cancer patients is focus on reducing the size of the tumor and improving operability, however, pCR is the most favorable effect in the short period [26-28]. Although the OS is not assured during the short period of follow-up, the pCR is reported to be a valuable surrogate measure for an improved long-term outcome, meanwhile patients without pCR indicates an increased risk of relapse and death [29-31].

It is known that trastuzumab and anthracyclines are both cardiotoxic drugs, thus the cardiotoxicity may be more severe when they are concurrently used [32-34]. According to this meta-analysis, the number of patients presented an asymptomatic absolute reduction in the LVEF of 10% had no significant difference in two groups. It is noted that almost all patients were stage II to III HER2-positive breast cancer, and the patients' median age were 48.5 (range: 21-71) and 46.8 (range: 25-75) in the concurrent and the non-concurrent use of trastuzumab and anthracycline-based NAC groups, respectively. The baseline LVEF of all patients were measured by multiple gated acquisition scan or echocardiography before NAC, and the baseline LVEF were favorable and similar in two groups. Based on the certain age and similar baseline LVEF, patients with the concurrent use of trastuzumab and anthracycline-based NAC didn't show more cardiotoxicity events compared to those with non-concurrent use of trastuzumab and anthracycline-based NAC.

Trastuzumab, a humanized monoclonal antibody, binds to the extracellular juxtamembrane

domain of HER2 and inhibits the proliferation and survival of HER2-dependent tumors [9]. The following mechanisms were considered to be action of anthracyclines in cancer cells. First, intercalate into DNA and lead to inhibit synthesis of macromolecules. Second, generate of free radicals and lead to DNA damage or lipid peroxidation. Third, initiate of DNA damage and apoptosis via inhibition of topoisomerase II [35]. Due to the different mechanisms of trastuzumab and anthracyclines, the concurrent use of them indicated an improved pCR rate in HER2-positive breast cancer. Although trastuzumab and anthracyclines were reported to be associated with an increased risk of cardiotoxicity, especially when concurrent use of them, previous studies [10-14] and this meta-analysis demonstrated that the concurrent use of trastuzumab and anthracycline-based NAC for certain HER2-positive breast cancer patients was both effective and well tolerated. The NOAH trial [12] compared the efficacy of the concurrent use of trastuzumab and anthracycline-based NAC, they reported pCR rate of 38% and 19% in the concurrent and non-concurrent use of trastuzumab and anthracycline-based NAC, respectively. Besides, trastuzumab was well tolerated despite concurrent use with anthracyclines [12], and trastuzumab was also cardiac safe during long-term assessment [36]. Therefore, the concurrent use of trastuzumab and anthracycline-based NAC should be considered for locally advanced HER2-positive breast cancer with closely monitoring the cardiac function.

Our meta-analysis of randomized controlled studies has demonstrated the pCR rate and cardiotoxicity of the concurrent use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer. To our knowledge, this study is the first meta-analysis of randomized controlled studies making a systematic evaluation about this controversial scientific topic. Meanwhile, this meta-analysis of randomized controlled studies has some limitations. Firstly, we searched several databases for eligible studies, but only five randomized controlled studies, including 443 HER2-positive breast cancer patients, were included. Besides, one study [12] had mixed patients of locally advanced and inflammatory breast cancer. Furthermore, although the NAC were all conducted with anthracycline-based regimens, the NAC regimens were not strictly the same in each included studies, and the durations of NAC were slightly different. Finally, the prognosis of long time survival was not analyzed in detail due to the short and different duration of follow-up in each study. We suggest that further research should be designed to make more understanding about these aspects.

Conclusions

Our meta-analysis of randomized controlled studies show that pCR rates are significantly higher in the concurrent use of trastuzumab and anthracycline-based NAC compared with the non-concurrent use of trastuzumab and anthracycline-based NAC for certain HER2-positive breast cancer patients, meanwhile without significantly increase of the cardiotoxicity. The available evidences support the concurrent use of trastuzumab and anthracycline-based NAC for certain HER2-positive breast cancer patients, meanwhile the cardiac function should be monitored closely.

Supplementary Material

Supplementary tables and appendix.

<http://www.jcancer.org/v09p3168s1.pdf>

Acknowledgements

Author Contributions

YTW, ZX, BA, JSW and KZ conceived and designed the study, conducted the study, provided methodological support, conducted the analyses, interpreted the results and wrote, read and edited the manuscript. YTW, LQK interpreted the results, read and edited the manuscript. HW, XL, HL, YCL, ZLW and KNW conducted the study and read and edited the manuscript. LQK conceived and designed the study, provided methodological support, interpreted the results, guided the analysis and read and edited the manuscript.

Funding

This study was funded by Graduate Student's Science Innovation Project of Chongqing (CYS16124) and National Natural Science Foundation of China (NSFC) (81372851).

Data sharing statement

All data are freely available online.

Trial registration number

PROSPERO (International prospective register of systematic reviews: <https://www.crd.york.ac.uk/PROSPERO/>), number: CRD42017071432.

Competing Interests

The authors have declared that no competing interest exists.

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