RESEARCH ARTICLE

Efficacy and Safety of Trastuzumab Added to Standard Treatments for HER2-positive Metastatic Breast Cancer Patients

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Abstract

Introduction: Trastuzumab, an HER2-targeting agents, has shown efficacy in metastatic HER2-positive breast cancer patients. Single-agent clinical trials have evaluated therapeutic regimens using trastuzumab for metastatic breast cancer patients. The aim of our study is to evaluate the efficacy and safety of trastuzumab in combination with chemotherapy or hormone therapy in HER2-positive metastatic breast cancer patients. Methods: A literature research was conducted in PubMed and to identify appropriate studies from relevant reviews. Randomized controlled trials comparing chemotherapy or hormone therapy regimens in combination with trastuzumab were eligible. Dadta on clinical outcomes, including safety, efficacy, and patient characteristics were collected. Results: Seven articles describing five trials were included in our systematic review and meta-analysis. Partners of trastuzumab included in trials were anthracycline, paclitaxel, docetaxel, anastrozole and letrozole. The addition of trastuzumab to chemotherapy improved the overall survival (HR=0.79, 95%CI 0.65-0.96), while to hormone therapy did not (HR=0.85 95%CI 0.56-1.30). All trastuzumab-containing regimens increased cardiac toxicity (RR=3.37, 95%CI 1.26-9.02) and grade III-IV adverse events. Conclusions: Our study supports the addition of trastuzumab to chemotherapy which is effective and tolerated for metastatic breast cancer with HER2+ patients. Of note, more adverse events will occur followed the use of trastuzumab, especially cardiac toxicity, with two treatment regimens.

Keywords: Trastuzumab - HER2-positive - metastatic breast cancer - chemotherapy - hormone therapy

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Introduction

Metastatic breast cancer (MBC) is a complication of primary breast cancer and has a 5-year survival rate of less than 25% (Horner et al., 2009). Proliferation and survival of epithelial cells is regulated in part by human epidermal growth factor receptors (HERs), one of which is HER2, also known as Neu and ErbB-2 encoded by the ERBB2 gene (Coussens et al., 1985). Amplification or over-expression of the ERBB2 gene occurs in 20-25% of women with metastatic breast cancers. HER2-positive MBC patients have aggressive disease and poorer outcomes than HER2-negative patients (Slamon et al., 1987). Trastuzumab (Herceptin) is a recombinant humanized monoclonal antibody that blocks the HER2 receptor, and is approved by the Food and Drug Administration approved it for treatment of metastatic breast cancer patients.

In 2001, trastuzumab demonstrated efficacy in combination treatment with a higher overall response rate and a longer survival over chemotherapy alone (Slamon et al., 2001). Subsequently, many phase II-III clinical trials have evaluated the efficacy of trastuzumab in combination with standard treatments (chemotherapy or hormone therapy) for HER2+ MBC patients, many of which were non-controlled clinical trials, while only several were randomized controlled trials (RCTs). Results have been inconsistent and more adverse events occur in combination regimens, such as cardiac dysfunction (Seidman et al., 2002), and isolated central nervous system metastases (Burstein et al., 2005). The overall benefit of trastuzumab added to chemotherapy or hormone therapy is uncertain. Therefore, we carried out a meta-analysis using data from RCTs to evaluate the efficacy and safety of trastuzumab used in association with standard treatments for metastatic HER2+ breast cancer patients.

Materials and Methods

Literature search

We searched the PubMed database using Mesh words and free text words in the search strategy. We applied the "trastuzumab [Supplementary Concept]", "herceptin" and "HER2 antibodies" for the trastuzumab and the search strategy below for metastatic breast cancer. Then we used sensitivity-and precision-maximizing version of the Cochrane Handbook for Systematic Reviews of Interventions (2008 revision) to filter RCTs (JPT et al.,

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2011). We also read the relevant reviews and systemic analysis to identify the relevant trials.

Metastatic breast cancer OR mbc OR ((secondary [Subheading] OR secondary [All Fields] OR metastatic [All Fields]) AND (breast neoplasms [mh] OR ((breast OR mammary) AND (cancer* OR neoplasm* OR carcinoma OR tumor* OR tumour*))))

Study selection

The studies had to meet the following inclusion criteria to enter the analysis:

1. The literature language was limited to English.
2. Randomized controlled trials whether blinded or not.
3. Comparison of a trastuzumab-containing regimen vs. standard treatment for metastatic breast cancer or advanced breast cancer patients with HER2 +.

The exclusion criteria below were used to exclude studies:

1. A second line of treatment.
2. Both treatment arms used trastuzumab for the concurrent and sequential therapy.
3. Trastuzumab vaccines or pharmacokinetic outcomes.
4. Other HER2 monoclonal antibodies.

Two individual investigators (Zhenli Zhu, Jun Zhang) scanned the titles and abstracts to remove obviously irrelevant articles and then read the full text of the potentially relevant articles. If there was a disagreement, a third investigator (Meilan Chen) would make a final decision. When a trial was reported for different times or several versions, we used the latest data and synthesized the data from different articles.

Data extraction and quality assessments

We extracted the data according to the Cochrane Handbook for Systematic Reviews of Interventions (JPT et al., 2011), which contained the trail ID, the first author, published year, study design, patient characteristics, test method for HER2 status, interventions and its dosage regimens, efficacy and safety endpoints and their outcomes. Then we assessed the risk of bias in included articles, according to Cochrane Handbook for Systematic Reviews of Interventions, which included random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting, and other potential biases. Two investigators (Zhenli Zhu, Jun Zhang) extracted the data and assessed the risk of bias independently and the discrepancies were resolved by discussion. Outcomes of interest were dichotomous variables such as overall response rate (ORR), clinical benefit ratio (CBR), time-to-event variables including time to progression (TTP) and overall survival (OS).

Statistical analyses

Time to progression and overall survival were our primary outcomes, plus ORR and CBR, to present the efficacy of the research arm (with trastuzumab) compared with the control arm, as well as adverse events which represented safety. Hazard ratio (HR) and associated variance were obtained indirectly from associated Kaplan-Meier curves using methods developed by Tierney (Tierney et al., 2007) for articles that do not report HR data directly. The minimum and maximum follow-ups were estimated and the HR and 95%CI were both calculated using the methods developed by Tierney (Tierney et al., 2007). For dichotomous variables, if there was a zero cell in a 2×2 table, we added a value 0.5 to each cell (Yusuf et al., 1985; Mantel et al., 2004). The study would be discarded from the outcome if there were two zero cells in a 2×2 table.

Intention to treat analysis was adapted in this meta-analysis. Homogeneity of effect size between studies was tested by Q statistics and a $P<.10$ was the level of significance. The I^2 statistic was calculated to quantitatively measure inconsistency between studies (Higgins et al., 2002; Higgins et al., 2003). Both fixed effect and random effect models were used in our analysis. When there was an $I^2 \geq 50\%$, the random effect model would be used. In a random effect model, there is variation between studies and the explanation of results would be more conservative (Yusuf et al., 1985; DerSimonian et al., 1986). Potential publication bias was tested by Begg funnel plots and Egger regression (Egger et al., 1997), and a sensitivity analysis was used to test the stability of the pooled results.

All analysis was performed by using the STATA version 12.0 software. A $P<0.5$ was considered statistically significant and all statistical tests were two-sided.

Results

Literature search

471 records were identified from the PubMed database and 44 records were derived from cited references. 452 records were excluded by screening abstracts and titles, most of which were reviews, comments or other monoclonal antibodies. We assessed the full-text of 50 relevant articles and 7 articles on 5 trials (three trials on chemotherapy (CH) and two on hormone therapy (HT)) were identified at the end. In these articles, three articles (Baselga et al., 2001; Eiermann, 2001; Slamon et al., 2001) reported the same trial. A flowchart was presented to show the selection process in this meta-analysis (Figure 1).

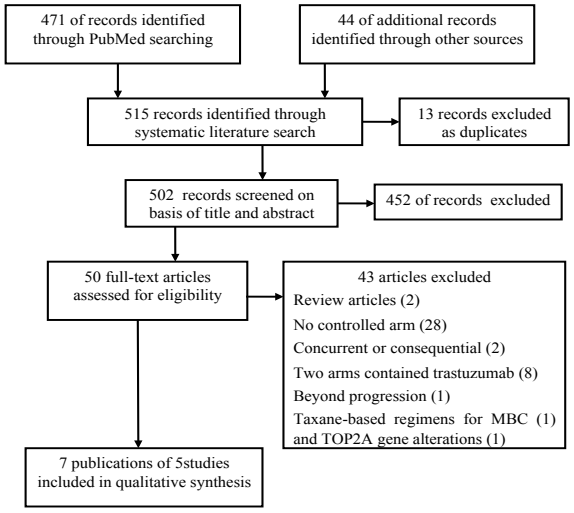

Figure 1. Flowchart of the Selection Process of the RCTs for Meta-analysis

Table 1. The Results of An Assessment for Bias in Included Trials

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other Potential Threats to Validity
Slamon	Unclear	Unclear	Inadequate	Adequate	Adequate	cross-over
Marty	Adequate	Unclear	Inadequate	Adequate	Adequate	cross-over
Gasparini	Adequate	Inadequate	Inadequate	Inadequate	Adequate	cross-over
Kaufman	Adequate	Unclear	Inadequate	Adequate	Adequate	cross-over
Huober	Adequate	Unclear	Inadequate	Adequate	Adequate	cross-over

Table 2. Characteristics of the Included Trials

Study	Treatment arm[1]	Dosage	Cycles	Patients age[2]	HER2 Status	Median follow
Slamon	Anthracycline (138)	Doxorubicin (60 mg/m^2) or epirubicin (75 mg/m^2) plus Cyclophosphamide (600 mg/m^2) every 3 weeks	6	54±10.1	IHC2+ or IHC3+	30 months
	Anthracycline (143)	Doxorubicin (60 mg/m^2) or epirubicin (75 mg/m^2) plus Cyclophosphamide (600 mg/m^2) every 3 weeks	6	54±10.3		
	Trastuzumab	4 mg/kg loading dose, 2 mg/kg weekly				
	Paclitaxel (96)	175 mg/m^2 every 3 weeks	6	51±11.0		
	Paclitaxel (92)	175 mg/m^2 every 3 weeks	6	51±11.5		
	Trastuzumab	4 mg/kg loading dose, 2 mg/kg weekly				
Marty	Docetaxel (94)	100 mg/m^2 every 3 weeks	6	55(24-79)	IHC3+ or FISH +	35.9 months
	Docetaxel (92)	100 mg/m^2 every 3 weeks	6	53(32-80)		40.9 months
	Trastuzumab	4 mg/kg loading dose, 2 mg/kg weekly	Until progression			
Gasparini	Paclitaxel (61)	80 mg/m^2 weekly	Until progression	54(30-71)	IHC2+ or IHC3+	16.6 months
	Paclitaxel (63)	80 mg/m^2 weekly	Until progression	56(32-72)		
	Trastuzumab	4 mg/kg loading dose, 2 mg/kg weekly				
Kaufman	Anastrozole (104)	1 mg daily	Until progression	54(27-77)	IHC3+ or FISH +	Not reported
	Anastrozole (103)	1 mg daily	Until progression	56(31-85)		
	Trastuzumab	4 mg/kg loading dose, 2 mg/kg weekly				
Huober	Letrozole (31)	2.5 mg daily	Until progression	61(47-88)	IHC3+ or FISH+	3.3 months
	Letrozole (26)	2.5 mg daily	Until progression	61.5(39-87)		14.1 months
	Trastuzumab	4 mg/kg loading dose, 2 mg/kg weekly after 2005, 8 mg/kg loading does, 6 mg/kg every 3 weeks				

[1]Drugs used (number of patients included in this arm); [2]Mean±SD, Median (range)

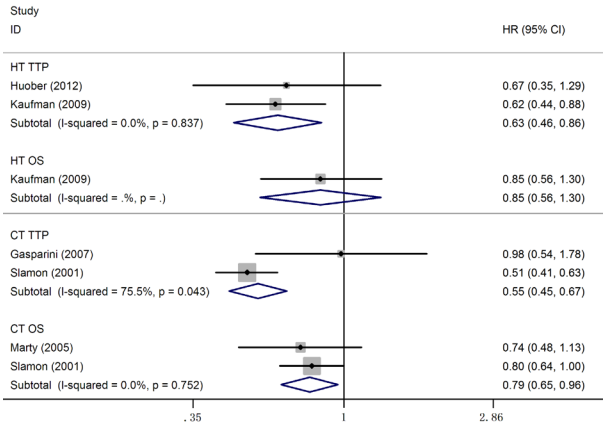

Figure 2. Forest Plot Representing the Pooled Results for OS and TTP. CT means chemotherapy with or without trastuzumab; HT means hormone therapy with or without trastuzumab

Study characteristics

The characteristics of included studies are summarized in Table 1. The five studies were published between 2001 and 2012, of which four were conducted in Europe and one in the United States. Patients with metastatic breast cancer or locally advanced breast cancer were included in these studies unless patients had central nervous system (CNS) metastasis. Patients were removed if they had accepted chemotherapy after metastasis, had another cancer, or had serious complications. All patients receiving first line therapy were included in this meta-analysis and patients experiencing progression after first-line trastuzumab therapy were excluded. The patients in included studies were required to have a baseline left ventricular ejection fraction (LVEF) greater than 50%, a measurable disease and a life expectancy. The HER2 status was tested by immunohistochemistry (IHC) (2+/3+) and/or fluorescence in situ hybridization (FISH) (≥2 ratios). There were two phase II trials and three phase III trials, all of which were open label trails.

Risk for bias

The assessment for bias was performed in accordance with the Cochrane Handbook (JPT et al., 2011) (Table 2). No trial presented the strategy for allocation concealment and all the trials were open label, which would not impact on the outcomes. When patients in the control group had experienced progression, they could across to the trastuzumab-containing group. Only Slamon's study reported the HER2 status was tested in a central laboratory and blinded to an independent response-evaluation committee (Slamon et al., 2001), while others did not. In Kaufman's study (Kaufman et al., 2009), patients who had received prior hormonal therapy for MBC were permitted and the sponsor controlled the database, performed all analyses, and interpreted the results. Huober's trial (Huober et al., 2012) was closed prematurely due to slow recruitment.

Efficacy

For the trials comparing chemotherapy with or without trastuzumab, there were two trials (Slamon et al., 2001; Marty et al., 2005) reported the OS data, and the pooled analysis demonstrated a 21% (RR=0.79, 95%CI 0.65-0.96) reduction in risk of death for patients in research arm. The pooled analysis on TTP (TTP defined as time from the

Table 3. Pooled Results for Adverse Events

Chemotherapy+/-trastuzumab						Hormone treatment+/-trastuzumab					
AEs	Trials	RR	95%CI	*P*[1]	I^2	AEs	Trials	RR	95%CI	*P*[1]	I^2
Alopecia	cde	1.07	0.97-1.18	0.205	43.90%	Arthralgia	ab	1.49	0.80-2.75	0.932	0%
Arthralgia	e	1.44	0.96-2.18	.	.	Bone pain	ab	1.56	0.65-3.71	0.317	0%
Diarrhea	cde	1.45	1.20-1.76	0.257	26.50%	Diarrhea	ab	2.99	1.46-6.12	0.472	0%
Dyspnea	ce	1.46	1.11-1.92	0.856	0%	Dyspnea	ab	1.21	0.57-2.57	0.246	
Fatigue	cde	1.18	0.90-1.55	0.013	0%	Fatigue	ab	4.1	0.59-28.70	0.142	53.70%
Headache	de	1.33	1.06-1.67	0.66	0%	Headache	ab	2.24	1.05-4.77	0.836	0%
Leukopenia	de	1.28	0.85-1.92	0.237	0%	Myalgia	a	4.96	0.59-41.61	.	.
Myalgia	de	1.06	0.81-1.39	0.994	0%	Nausea	ab	3.64	1.52-8.71	0.782	0%
Nausea	cde	1.04	0.92-1.17	0.629	0%	Paresthesia	a	3.58	0.40-32.36	.	.
Paresthesia	de	1.34	1.04-1.74	0.463	0%	Pyrexia	ab	2.85	1.32-6.15	0.601	0%
Pyrexia	cde	1.79	1.46-2.20	0.64	0%	Stomatitis	a	8.3	0.45-153.61	.	.
Rash	de	1.89	1.40-2.55	0.774	0%	Vomiting	ab	4.05	1.82-9.00	0.665	0%
Stomatitis	e	1.06	0.75-1.51	.	.						
Vomiting	cde	1.18	0.98-1.42	0.712	0%						

[1]*P* value belongs to RR; a, J Huober's study; b, Kaufman's study; c, Gasparini' study; d, Marty's study; e, Slamon's study

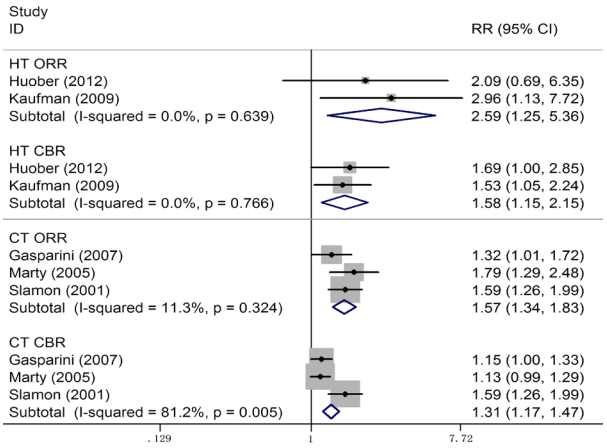

Figure 3. Forest Plot Representing the Pooled Results for ORR and CBR. CT means chemotherapy with or without trastuzumab; HT means hormone therapy with or without trastuzumab

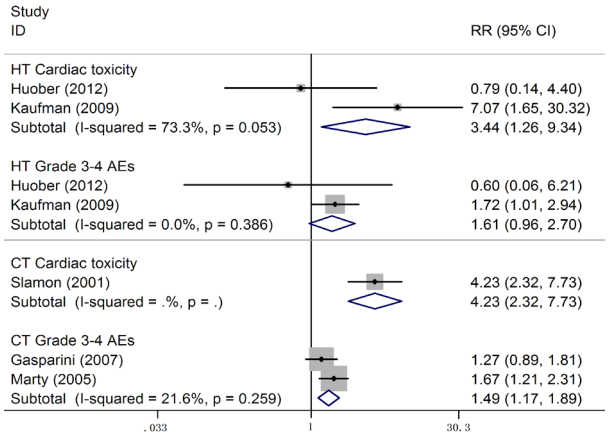

Figure 4. Forest Plot Representing the Pooled Results for Cardiac Toxicity and Grade III-IV Adverse events. CT means chemotherapy with or without trastuzumab; HT means hormone therapy with or without trastuzumab

date randomized to date of progression) showed a benefit in favor of trastuzumab-contained arms (HR=0.66, 95%CI 0.35-1.25) with a significant heterogeneity (P=0.043 I^2=75.5%) (Figure 2). There was an increased ORR in research arm compared to control arm by 57% (RR=1.57, 95%CI 1.34-1.83). There was significant heterogeneity across trials for the CBR (P=0.005 I^2=81.2%) and a benefit in favor of research arms (RR=1.25, 95%CI 1.01-1.56) (Figure 3). There was also a benefit for patients receiving trastuzumab and hormone therapy compared with hormone therapy alone, for TTP (HR=0.63, 95%CI 0.46-0.86) (Figure 2), ORR (RR=2.59, 95%CI 1.25-5.36) and CBR (RR=1.58, 95%CI 1.15-2.15) (Figure 3). Only one trial (Kaufman et al., 2009) reported the OS data and it showed a benefit of 15% to reduce the death risk with a 95%CI (0.56-1.30).

Safety

For the trials comparing chemotherapy with or without trastuzumab, there is only one trial (Slamon et al., 2001) reported the cardiac toxicity (Figure 4) with an increased incidence 323% (95%CI 2.32-7.73) for research arm patients. In hormone therapy and trastuzumab groups, an increased cardiac toxicity was also found (RR=2.48, 95%CI 0.28-21.85), with heterogeneity (*P*=0.053 I^2=73.3%). Cardiac toxicity is a common adverse event to patients had received trastuzumab, therefore we did a pooled analysis for all the trials (Seidman et al., 2002). Three trials (Slamon et al., 2001; Kaufman et al., 2009; Huober et al., 2012) reported data about the cardiac toxicity. The pooled analysis for cardiac toxicity demonstrated that more patients in research arm experienced adverse cardiac events than patients receiving standard treatments alone (RR=3.37, 95%CI 1.26-9.02), with heterogeneity (*P*=0.132 I^2=50.6%).

Grade III-IV adverse events (Figure 4) were reported in four trials comprised of two hormone therapy trials (Kaufman et al., 2009; Huober et al., 2012) (RR=1.61, 95%CI 0.96-2.70) and two chemotherapy trials (Marty et al., 2005; Gasparini et al., 2007) (RR=1.49, 95%CI 1.17-1.89) (Figure 4). All four trials reported a decrease in LVEF in the treatment arms with trastuzumab. The risk for more adverse events was compared between two treatment arms as shown in Table 3.

Sensitivity analysis and publication bias

There is no sensitivity and publication bias analysis in this article for a few eligible trails included.

Discussion

Our study shows that the combination of trastuzumab with chemotherapy or hormonal therapy improves the OS and TTP compared to standard treatment alone for women with HER2-positive metastatic breast cancer. This is consistent with results form a meta-analysis of HER2-targeted agents in MBC (Harris et al., 2011). However, in our study, patients receiving trastuzumab and hormone therapy may benefit on OS (HR=0.85 95%CI 0.56-1.30). Patients in the hormone therapy group could be administered trastuzumab in combination with hormone therapy when they experience progression, which could account for the reduced impact of trastuzumab on OS for patients on hormone therapy. There was an obvious heterogeneity when pooled TTP in chemotherapy trials and the reason could be due to the different number of patients or different chemotherapy drugs used (anthracyclines or paclitaxel). There was also significantly heterogeneity for the same reason when CBR was pooled.

All the trials reported adverse events. Pooled analysis for grade III-IV adverse events demonstrates that risk increased by 49% and 61% for patients in the trastuzumab treatment arms, respectively (Figure 4). As shown in Table 4, patients in the trastuzumab-containing arms experience more adverse events compared to controls, which may partly be due to the longer follow up time for patients in the trastuzumab arms. The pooled analysis for cardiac toxicity demonstrates that the incidence of cardiac toxicity increase in both the trastuzumab/hormone therapy and trastuzumab/chemotherapy arms. In two trials (Slamon et al., 2001; Marty et al., 2005), we find that cardiac toxicity happened more frequently in patients who receive concurrent or prior anthracyclines treatment in combination with trastuzumab, with one patient dying from cardiac dysfunction. Keefe (2002) reports that the risk of cardiotoxicity with trastuzumab is 27% when administered in combination with anthracycline and cyclophosphamide, but severe outcomes were uncommon. In another review (Ewer et al., 2007), severe congestive heart failure was reported in 2% of patients and ejection fraction declines in 6%-18% of patients with metastatic breast cancer who used trastuzumab-related regimens. For MBC patients, trastuzumab should not be administered in combination with anthracycline according to the advice from European Agency for the Evaluation of Medical Products and trastuzumab should be used with caution in patients who have prior or current use of anthracycline. However, a docetaxel/carboplatin/trastuzumab triple combination can offer clinical efficacy with low risk of cardiac dysfunction in patients with HER2+ MBC (Andersson et al., 2011), and symptomatic cardiac events are infrequent when trastuzumab is administered with vinorelbine (Chan, 2007).

In this meta-analysis, all trials included were open label, and MBC patients in the standard treatments alone group could cross over to the trastuzumab-combination treatment group at the point of disease progression. For the reasons mentioned above, the impact on efficacy and safety of combination therapy would be underestimated compared to chemotherapy or hormonal therapy alone. Differing methods to determine HER2 status, as well as the time of testing, may also impact the results. Only one trial (Slamon et al., 2001) reported the status of HER2 was tested by central laboratory, and IHC was used in almost all trials included in this meta-analysis. In another review, the author suggested that IHC is the suitable method for obviously negative cases (0 and 1+), whereas FISH is the method that more accurate, reliable, and precise test for confirming or excluding the HER2 test in indeterminate 2+ and 3+ cases (Cuadros et al., 2009). In these trials, the dosages of trastuzumab were similar, but dosages of other drugs were different between trials, which resulted in some heterogeneity across trials as well as different schedules being used.

There were only five RCT trials included in our final meta-analysis, two trials on hormone therapy and three with chemotherapy. Though we retrieved more than 50 articles, more phase II trials evaluated regimens consisting of cytotoxicity drugs and trastuzumab, most of which were single-arm trials and included small numbers of patients. From our study, we can find that there are only several combination regimes (anthracycline, paclitaxel, docetaxel, anastrozole and letrozole) assessed by RCT design. The addition of trastuzumab to these drugs demonstrates the efficacy, but does not mean the combination of other cytotoxicity drugs and trastuzumab would benefit MBC HER2+ patients (Chan, 2007). Many drugs have not been assessed by RCT design in combination with trastuzumab for MBC patients with HER2+, but combined regimens are prescribed widely, such as gemcitabine (O'Shaughnessy et al., 2004). Another problem is finding the optimal combined regimen for these patients though clinical trials (Wardley et al., 2010; Valero et al., 2011).

This meta-analysis has some limitations. There were only two and three trials in each kind of study and the total number of patients in meta-analysis was merely 1000. We did not contact the authors of the trials included in our study to retrieve unpublished data and individual patient data. The reported outcomes of endpoints varied across the trials, for example, the variation in median duration of TTP or HR and P for TTP, therefore we used the estimated value if we could or as it missing value.

This is the first time meta-analysis has been used to evaluate the efficacy and safety of trastuzumab in combination with chemotherapy or hormone therapy. This meta-analysis was made grimly according to the Cochrane Handbook for Systematic Reviews of Interventions (JPT et al., 2011) and the report was written in accordance with the PRISMA statement (Moher et al., 2009).

In Conclusion: Our study suggests the addition of trastuzumab to chemotherapy or endocrine therapy enhances effective and is well tolerated. More adverse events will occur following the use of trastuzumab, especially cardiac toxicity, which requires attention. In further trials, quality of life should be included among the outcomes. More well-designed RCTs are needed to determine the optimal therapy regimen for MBC patients positive for HER2.

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