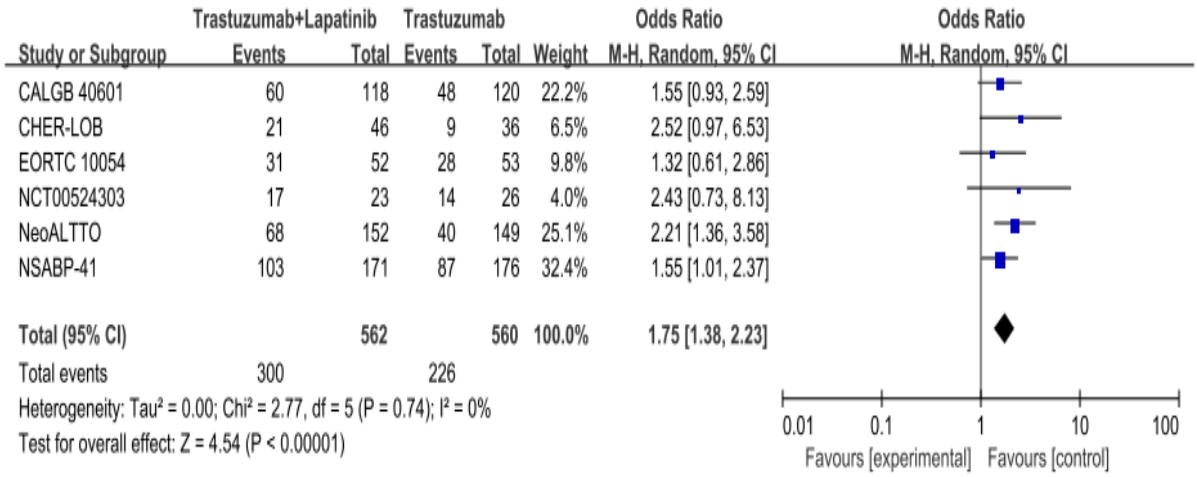

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Meta-analysis

Lapatinib, trastuzumab or the combination added to neoadjuvant chemotherapy for breast cancer

Quan Liang[1], Qiang Fu[1], Wei Li[2], Jiacong You[3] and Zhanchao Zhao[1]

[1]Department of General Surgery; [2]Department of Ultrasonography; [3]Tianjin Lung Cancer Institute, Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Tianjin Medical University General Hospital, 154 Anshan Road, Heping District, Tianjin 300-052, China.

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Abstract

The aim of this study was to compare the efficacy and safety of trastuzumab versus the combination of trastuzumab and lapatinib added to neoadjuvant chemotherapy for f breast cancer. PubMed, MEDLINE, The Cochrane Library, Web of Science and nearly 5 years of the important international conference on oncology records were searched for randomized clinical trials that compared lapatinib plus trastuzumab and neoadjuvant chemotherapy (NAC) with trastuzumab in combination with NAC and that included pathologic complete response rate as the primary outcome. Finally, 6 clinical randomized controlled trials were included. Meta-analysis shows that pathological complete response rate was significantly increased in trastuzumab plus lapatinib group than single use trastuzumab group (53.4%, 40.4%, RR = 1.75, 95% CI 1.38 ~ 2.23, p<0.001). In conclusion, the combination of trastuzumab and lapatinib added to neoadjuvant chemotherapy in HER2-positive breast cancer is more effective.

Introduction

With the application of the trastuzumab which is the first target drug for human epidermal growth factor receptor 2 molecular, overall survival in patients with HER2-positive breast cancer has been significantly improved (Ross et al., 2009; Dawood et al., 2009). Trastuzumab in breast cancer neoadjuvant therapy (Gianni et al., 2011) and adjuvant therapy (Viani et al., 2007) and metastasis of breast cancer (Harris et al., 2011) can make patients benefit from this has now been confirmed.

In terms of survival and overall disease progression, neoadjuvant chemotherapy for the treatment of breast cancer has been reported to be equivalent to adjuvant chemotherapy (Mauri et al., 2005). Besides, neoadjuvant chemotherapy offers certain benefits, since it can decrease the primary tumor in the majority of patients, increasing breast-conserving surgery (BCS) rates or improving respectability (Huang et al., 2009). Lapatinib as the second listed anti-HER2 target drug is combined with capecitabine, this has become the standard first-line treatment of advanced HER2-positive metastatic breast cancer patients (Geyer et al., 2006). For HER2 over-expressing breast cancer, preoperatively given target of anti-HER2 treatment can significantly inhibit the proliferation of tumor, reduce tumor residual after treatment and increase the probability of breast conserving surgery and improve resectability and for evaluation of tumor response to chemotherapy by changes in tumor size (Jackisch et al., 2015; Gianni et al., 2014; Badwe et al., 2011).

Given the promising results of trials that evaluated the addition of lapatinib to trastuzumab in metastatic disease (Blackwell et al., 2012), multiple studies have been aimed at evaluating the clinical benefit of adding lapatinib to trastuzumab plus chemotherapy for operable HER2-positive breast cancer in neoadjuvant

settings; results have been conflicting. So, to evaluate the efficacy of adding lapatinib to trastuzumab combined with neoadjuvant therapy for the treatment of HER2-positive breast cancer, a meta-analysis of all relevant published randomized clinical trials (RCTs) was performed.

Materials and Methods

Eligibility criteria

Have been published regarding the use of patients with HER2-positive breast cancer neoadjuvant chemotherapy combined with trastuzumab compared neoadjuvant chemotherapy combined with trastuzumab, lapatinib dual targeting drug efficacy and safety of stage II or III prospective random control research. The test group was neoadjuvant chemotherapy plus trastuzumab plus lapatinib. The control group was neoadjuvant chemotherapy plus trastuzumab. There was no restriction on neoadjuvant chemotherapy, but for the same study, the test group and the control group were the same as the new adjuvant chemotherapy, only anti-HER2 treatment was different. The primary outcome was a pathological complete response (pCR).

Exclusion criteria

i) The study of non-operative advanced breast cancer; ii) Non-prospective randomized controlled trial; iii) Baseline balance between the test group and the control group was poor, and they were not comparable between the two groups; iv) Study on the evaluation index of curative effect; v) High rate of loss of follow-up, more than 10% of the study; vi) The follow-up study was less than 2 years.

Search strategy

Computer retrieval PubMed, Medline, The Cochrane Library, Web of Science, Chinese journal full-text database and Wan Fang Medical journal full-text database, plus nearly 5 years of the important international conference on oncology records retrieval time was limited up to July in 2015. The language was not limited. When the same research had a number of literature reports, only the latest and most recent literature was evaluated. Key words were breast cancer, neoadjuvant, trastuzumab and lapatinib, breast cancer, neoadjuvant chemotherapy and according to the reference literature expand the search.

Data extraction

By two researchers independently, encounter differences through discussion, access to the original data or consult the relevant experts to solve. Data extraction includes: The first author's name, year of publication, the number of cases could be evaluated the efficacy of intervention measures, and indicators, etc.

Quality control

To assess the validity of the included studies, according to the Cochrane handbook, we examined the sequence generation of allocation, allocation concealment, masking of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting.

Statistical analysis

Meta software RevMan 5.0 was used for statistical analysis. For each included study, we will calculate risk ratio (RR) and 95% confidence intervals (95% confidence interval, 95% CI). The Q-statistic was used to test heterogeneity between trials. The presence of statistical heterogeneity was assessed using Cochran's Q test and quantified using I^2 and respective 95% CI. $p<0.10$ was considered to indicate a statistically significant difference. For the I^2 values, ≥50% indicated a large heterogeneity. No obvious heterogeneity across studies using random effects model, the Mantel-Haenszel meta-analysis; obvious heterogeneity exists, the first analysis of heterogeneity produces the reason, after treatment, the heterogeneity can't be eliminated, we will use subgroup analysis.

Results

Literature selection and study characteristics

The process of identifying eligible trials is presented in Figure 1. According to the above retrieval strategy initially obtained 476 articles, after eliminating duplicate documents retained 450. By reading the title and abstract, excluding the review, case report, retrospective study, observational studies and intervention measures did not meet the inclusion criteria of literature and 30 articles. Six eligible full-text articles were retrieved, all of which were randomized controlled trials and from peer-reviewed studies. These trials were included in the meta-analysis. The basic characteristics of the 6 trials included are shown in Table I. The assessment of the quality of each study is shown in Table II.

The results of meta-analysis

A total of 1143 patients (n=574, in the lapatinib plus trastuzumab arm and n=569, in the trastuzumab arm) from 6 studies (13-18) were analyzed for the effect of adding lapatinib to trastuzumab plus NAC on the pCR rate in breast cancer. The absolute pCR rate was estimated to be 40.4% in the trastuzumab alone arm and 53.4% in the combination arm using random-effects meta-analysis modeling. The odds of pCR in the breast were 1.75 times higher for the combination arm (95% CI: 1.38–2.23; $p<0.00001$; heterogeneity test: $p=0.74$; $I^2 = 0\%$) (Figure 2).

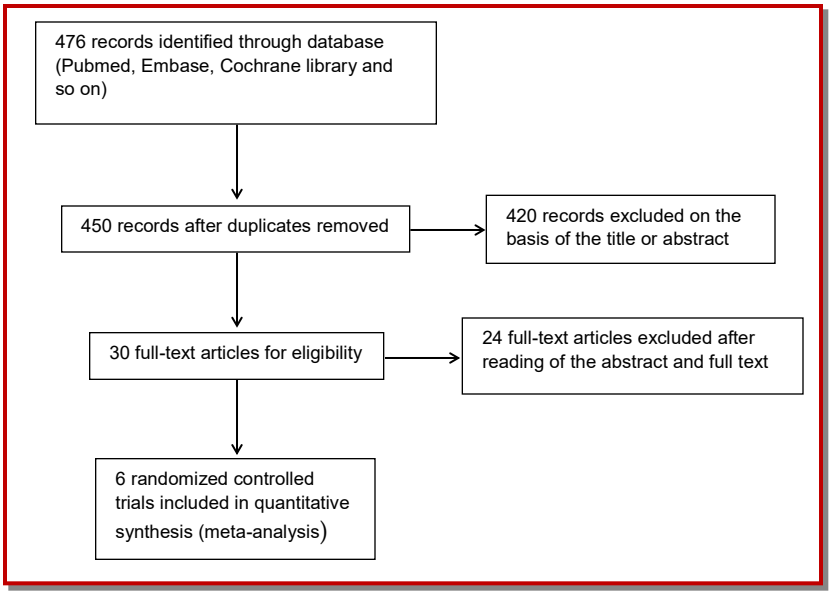

Figure 1: Flow-chart diagram of study selection. Finally, six eligible full-text articles were retrieved

Table I

Characteristics of eligible trials

Clinical trial (reference)	Number of patients, n	HER2 status assessment	Neoadjuvant chemotherapy duration (week)	Participants enrolled (n)	Neoadjuvant anti-HER2 therapy
CHER-LOB (Guarneri et al., 2012)	121	IHC(3+) OR FISH(+)	26	39 36 46	L1500 mg/d T4 mg/kg/w→2 mg/kg/w L1000 mg/d +T2 mg/kg/w
NCT 00524303 (Holmes et al., 2013)	100	IHC(3+) OR FISH(+)	26	34 33 33	L1250 mg/d T4 mg/kg/w→2 mg/kg/w L750 mg/d +T2 mg/kg/w
Neo ALTTO (de Azambuja et al., 2014)	455	IHC(3+) OR FISH(+)	18	154 149 152	L1500 mg/d T4 mg/kg/w→2 mg/kg/w L1000 mg/d +T2 mg/kg/w
NSABP-41 (Robidoux et al., 2013)	524	IHC(3+) OR FISH(+)	12	173 178 173	L1250 mg/d T4 mg/kg/w→2 mg/kg/w L750 mg/d +T2 mg/kg/w
CALGB40601 (Carey et al., 2013)	305	IHC(3+) OR FISH(+)	16	67 120 118	L1500 mg/d T4 mg/kg/w→2 mg/kg/w L750 mg/d +T2 mg/kg/w
EORTC10054 (Bonnefoi et al., 2015)	128	IHC(3+) OR FISH(+)	18	23 53 52	L1000 mg/d T4 mg/kg/w→2 mg/kg/w L1000 mg/d +T2 mg/kg/w

Discussion

HER2 amplification in breast cancer is a classic example of oncogene addiction in solid tumor oncology (Olson, 2012). Recent studies suggest that dual HER2 inhibition (the administration of two anti-HER2 therapeutics simultaneously) may induce more durable tumor responses than sequential HER2 specific monotherapy (Blackwell et al., 2010). The study systematically collected HER2-positive breast cancer patients treated with neoadjuvant chemotherapy combined with trastuzumab, lapatinib dual anti-HER2 therapy compared with neoadjuvant chemotherapy plus trastuzumab randomized controlled trial evidence. This evidence support HER2-positive breast cancer treated with neoadjuvant chemotherapy combined with anti-HER2 dual targeting drug. Trastuzumab and lapatinib have effects on different parts of the HER2 receptor,

Table II

Quality control						
Clinical trial	Sequence generation of allocation	Allocation concealment	Masking of participants	Personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting
CHER-LOB [13]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
NCT 00524303 [14]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Neo ALTTO [15]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
NSABP-41 [16]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
CALGB40601 [17]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
EORTC10054 [18]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk

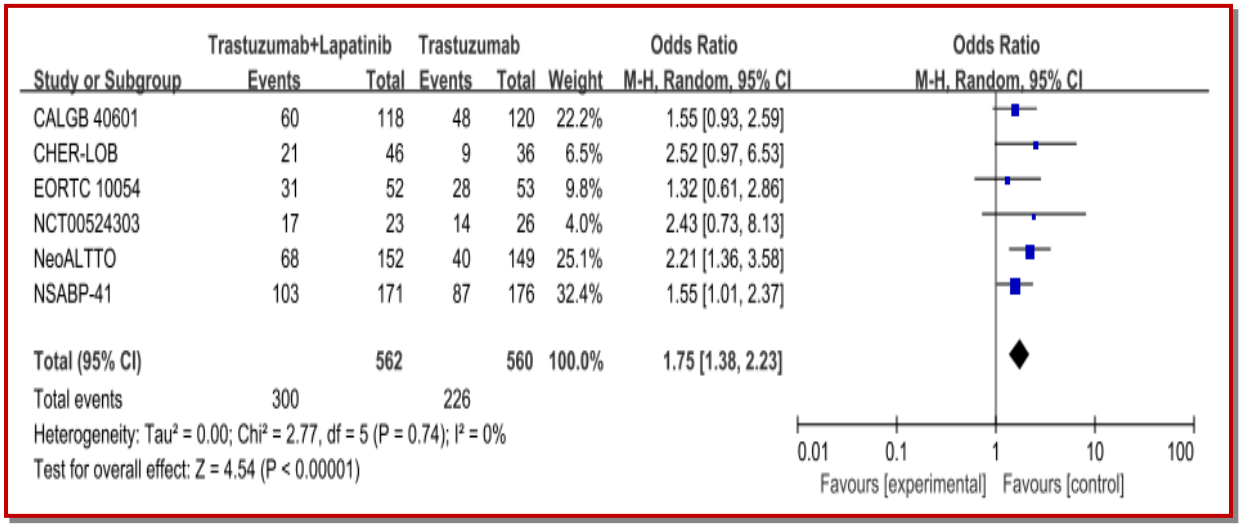

Figure 2: The results of meta-analysis

their principle and mechanism can complement each other, a pre-clinical study has confirmed the combined use of the two drugs can dramatically inhibit the growth of breast cancer cells, enhancement of HER2 blocking effect (Konecny et al., 2006). In addition, more thorough and more comprehensive anti-HER2 therapy seems to reduce the resistance of HER2 (Wang et al., 2011). That trastuzumab, lapatinib double anti-HER2 drugs cure HER2-positive metastatic breast cancer, which have been confirmed in clinical therapy (Blackwell et al., 2012). Pertuzumab and trastuzumab are complementary in the anti-HER2 mechanism, which is same as lapatinib. Combination pertuzumab with trastuzumab for the first-line treatment of HER2-positive metastatic breast cancer is very effective, which has been confirmed in clinical therapy too (Baselga et al., 2012). The meta-analysis also has some limitations. Firstly, the relatively small number of the case in the study may affect the statistical conclusion. But in order to be able to collect all randomized controlled trials, the author has systematically screened all the possible candidates for randomized controlled study. Secondly, due to the inability to get the survival data in the case of, we are not able to assess the higher pCR rate patients whether have longer survival in the study. However, pCR as independent prognostic factors of survival benefit, this has been confirmed on HER2-positive breast cancer patients after anti-HER2 therapy (Doval et al., 2013; Untch et al., 2011). Neoadjuvant studies using anti-HER2 agents have revealed that the pCR rate is correlated with disease-free survival (Gianni et al., 2010; Untch et al., 2011).

Conclusion

This study demonstrates that the use of trastuzumab in the neoadjuvant therapy combined with lapatinib dual targeting of anti-HER2 therapy can significantly increase the pCR rate in the HER2-positive breast cancer patients. But a combination of targeted drugs in the double neoadjuvant treatment of HER2-positive

breast cancer can take advantage of pCR to prolong disease-free survival or overall survival, still need further verification.

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Conflict of Interest

Authors declare no conflict of interest

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Author Info
Zhanchao Zhao (Principal contact)
e-mail: liangq01@126.com