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Optimum duration of adjuvant trastuzumab in treatment of human epidermal growth factor receptor-2 positive early breast cancer: protocol for a network meta-analysis of randomized trials

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Abstract

Introduction: Controversy regarding optimum duration of trastuzumab treatment remains in patients with human epidermal growth factor receptor-2 (HER2) positive early breast cancer. Our purpose of this network meta-analysis (NMA) is to synthesize all available evidence based on direct and indirect comparisons of efficacy and safety to identify the duration of trastuzumab treatments with the greatest value in HER2 positive early breast cancers.

Methods and analysis: Electronic searches of titles/abstracts of trastuzumab treatments for early breast cancers will be performed, using PubMed, Cochrane Library, Embase and ClinicalTrils.gov from inception to June 16, 2019, as well as the annual meetings of San Antonio Breast Cancer Symposium (SABCS), European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) online archives. The outcomes of interest are overall survival, disease-free survival, acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities. Two independent reviewers will screen and extract eligible data based on the inclusion and exclusion criteria, and then assess the risk of bias and quality of evidence of individual study using Cochrane Collaboration's tool and GRADE (Grades of Recommendation, Assessment, Development and Evaluation), respectively. The heterogeneity, transitivity and inconsistency of NMA will be assessed.

We will plan subgroup and sensitivity analyses to assess the robustness and reliability of findings in our NMA.

Ethics and dissemination: This study synthesizes the evidence regarding optimum duration of trastuzumab treatment in patients with HER2 positive early breast cancer. We hope the findings from our study will help clinicians to reduce the uncertainty of escalating and de-escalating duration treatment and select optimum duration of trastuzumab treatment with the most value in terms of efficacy and safety. Findings from our NMA will be disseminated through international conference reports and a peer-reviewed journal.

Ethics approval is not required for our NMA.

Strengths and limitations of this study

- Our purpose of this NMA is to synthesize all available evidence based on direct and indirect comparisons of efficacy and safety to identify the duration of trastuzumab treatments with the greatest value in HER2 positive early breast cancers.
- We hope the findings from our study will help clinicians to reduce the uncertainty of escalating and de-escalating duration treatment and select optimum duration of trastuzumab treatment with the most value in terms of efficacy and safety.
- We will plan subgroup and sensitivity analyses to assess the robustness and reliability of findings in our NMA.

- The limitations of our study might be related to language bias, due to this NMA will only include studies published in English.

Trial registration number CRD42019139109

Keywords: early breast cancer, human epidermal growth factor receptor-2, trastuzumab, network meta-analysis, protocol

Introduction

Human epidermal growth factor receptor-2 (HER2) positive breast cancer accounts for approximately 20–25% of overall reported cases[1 2] and is correlated with poor prognosis.[3 4] Trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 protein, is indicated for use in patients with HER2-positive early breast cancer.[5-7] At present, a 1-year of trastuzumab for targeted therapy has been proven to significantly improve overall survival (OS) and disease-free survival (DFS) in early HER2-positive breast cancer.[8-11]

However, the optimal duration of trastuzumab treatment is an intense controversy and ongoing debate area in terms of efficacy, toxicity, convenience and cost.[12] Nevertheless, a considerable gap exists in the current literature. High-quality randomised controlled trials (RCTs) confirmed that multiple treatment durations of trastuzumab were effective treatments for HER2-positive early breast cancers, but not all head-to-head trials were performed to evaluate relative efficacy and safety. The HERceptin Adjuvant (HERA) trial confirmed that 24 months of adjuvant trastuzumab did not improve DFS compared with 12 months of adjuvant therapy [hazard ratio (HR) 1.02, 95% confidence intervals (CI) 0.89–1.17], at a higher cost, inconvenience and cardiac toxicity (7.3% vs 4.4%).[13] On the contrary, six months of this drug was non-inferior and decreased cardiac toxicity (8% vs 4%, P<0.001) in the PERSEPHONE trial, but the results were not shown as non-inferior in the

PHARE and HORG trials compared with 12 months of trastuzumab treatment.[14-16] Differently, the SOLD and Short-HER trials conducted that nine weeks of trastuzumab was not non-inferior to 12 months of trastuzumab, but a significant reduction in cardiac toxicity was observed with nine weeks of trastuzumab.[17 18]

As mentioned above, there was a little direct comparison among preventive strategies due in part to half of RCTs including N9831, NSABP-B31, BCIRG 006 and FinHER trials compared active therapy to inactive interventions (e.g., placebo).[10 11 19] Several pivotal pairwise meta-analyses evaluated the direct efficacy and toxicity between shorter durations of trastuzumab and standard option, and addressed that 12 months of trastuzumab was still considered the optimal treatment for early HER2-positive breast cancer, with a significant increase in cardiac events.[12 20-23]

These intriguing results sparked a heated debate about whether escalating and de-escalating duration treatment can be considered new standard of care. Network meta-analysis (NMA) has indirectly evaluated relative efficacy and toxicity of multiple durations of adjuvant trastuzumab therapies in HER2-positive early breast cancer. To address the aforementioned debate problems and provide the best available treatments, our purpose of this NMA is to synthesize all available evidence based on direct and indirect comparisons of efficacy and safety

to identify the duration of trastuzumab treatments (24 months vs 12 months vs 6 months vs 12weeks vs 9 weeks vs placebo) with the greatest value in HER2 positive early breast cancers.

Methods

The results of our protocol will be evaluated in line with the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols).[24] Similarly, we will perform this NMA with the methods guided by the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions.[25] The project has been registered in PROSPERO (CRD42019139109).

Search strategy

Electronic searches of titles/abstracts of trastuzumab treatments for early breast cancers will be performed, using PubMed, Cochrane Library, Embase (Ovid interface) and ClinicalTrils.gov, as well as the annual meetings of San Antonio Breast Cancer Symposium (SABCS) (2015-2019), European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) online archives until June 16, 2019. Additional RCTs related to the topic will be included after their publication. Two reviewers who have been trained in data extraction will independently conduct search strategies. The same two authors will manually search reference lists from eligible reviews and relevant trials to

identify additional potential studies. We will record the reason for excluding the full text and generate a PRIMSA flow diagram for the NMA.[26]

The search terms will include the following domains of Medical Subject Heading (MeSH) terms: 'breast cancer', 'human epidermal growth factor receptor-2' and 'trastuzumab', according to PICOS (Population Intervention Comparison Outcomes Study Design) statement. MeSH and Subheadings were combined with 'AND' or 'OR'. The complete search strategy is presented in online supplementary file 1 (see the appendix 1).

We will perform a pilot test to evaluate inter-rater reliability and adjust each screening stage: title and abstract, followed by full-text screening. Two independent reviewers will screen the titles/abstracts of related studies based on an inclusion and exclusion criteria. The eligible or potentially eligible trials will be assessed by reading through the full texts when necessary. Moreover, disagreements in data extraction will be resolved via having a discussion, with the help of the third reviewer.

Eligibility criteria

Trials will be eligible if they adhere to the following criteria: 1. Populations: HER2-positive early breast cancer of any age or nationality, treated with trastuzumab treatments; 2. Interventions: Any duration of trastuzumab treatments being given. We are also interested in the impact

of placebo/observation as adjuvant treatment; 3. Comparators: all eligible interventions with one another; 4. Outcomes: OS, DFS, acceptability, and cardiotoxicities and grade 3-4 nonhematologic toxicities; 5. Study design: RCTs that compared any two or more different arms of adjuvant trastuzumab in patients with HER2-positive early breast cancer; 6. Language and other limitations: We will include studies published in English without date limited.

Studies not meet the inclusion criteria will be excluded. The other excluding criteria are as follows: 1. neoadjuvant and adjuvant treatment with trastuzumab biosimilars; 2. Palliative care with trastuzumab; 3. Retrospective and prospective cohort studies.

Outcomes

The outcomes of interest are OS (defined as the time from randomization to death from any cause), DFS (defined as the time from randomization to local, regional, distant relapse, contralateral breast cancer, second primary cancer, or death from any cause, whichever occurred first), acceptability (defined as the proportion of patients who discontinued trastuzumab), and cardiotoxicities and grade 3-4 nonhematologic toxicities. The cardiac toxicity grading is used by the Common Terminology Criteria for Adverse Events of the National Cancer Institute. Cardiac toxicity is defined as an asymptomatic decline in left ventricular ejection fraction (LVEF) to ≤45%, an absolute drop of

10-15% in follow-up echocardiography, symptomatic congestive heart failure (New York Heart Association [NYHA] class III/IV) or cardiac death.[27 28] We will calculate the relative effectiveness for each network comparison among all duration of treatments with trastuzumab.[29]

Data extraction and management

The management of literature search records will be carried out in EndNote X7. A spreadsheet will be created in Microsoft Excel 2010 (Microsoft Corp, Redmond, WA, www.microsoft.com) to collect outcomes of interest, such as, study ID, first author, study design, recruitment time frame, detailed interventions, sample size, and endpoints (OS, DFS, acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities). We will attempt to contact study authors and relevant pharmaceutical companies if important data are not reported. If duplicate publications are identified, the update data will be included.

Bias risk

According to the following domains outlined in the Cochrane Collaboration's tool, for the risk of bias of RCTs in the NMA the following domains will be evaluated in Review Manager (version 5.3):[30] random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other bias. Two authors will independently review RCTs and report a high risk of bias "-", a low risk of bias "+", or an unclear risk

of bias "?". Any disagreements in assessment of risk of bias will be resolved by discussion, or the help of the third reviewer if needed.

Quality of evidence

We will assess the quality of evidence of individual study using GRADE (Grades of Recommendation, Assessment, Development and Evaluation), which is based on the following five domains: risk of bias, imprecision, inconsistency, indirectness and publication bias.[31 32] The staging system categorizes for GRADE evidence are scored as high, moderate, low or very low quality. The initial confidence level for each RCT is high, but will be rated down based on the evaluation of the five domains. The strength of evidences will be graded for the outcomes based on GRADE system in CINeMA.

Statistical analysis

We will perform the traditional pairwise meta-analysis on direct comparisons based on two or more studies with Stata13.0 (StataCorp, College Station, TX, USA). To directly and indirectly compare between any eligible interventions, NMA for outcomes of interest is planned using WinBUGS version1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

Results regarding the OS and DFS are calculated HR with 95% confidence intervals CI. Binary outcomes (acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities) are expressed as odds ratios (ORs) with 95% CI. The results of probability statements of intervention

effects will be ranked. The interventions with surface under the cumulative ranking (SUCRA) of being the most effective in term of efficacy and safety will be evaluated to interpretation of relative effect of comparisons. The benefit-risk analysis of efficacy and toxicity within each comparison will also be completed. Two sided $P < 0.05$ is considered significant.

We will estimate the presence of heterogeneity based on the magnitude of I^2 estimated from pairwise meta-analysis models. If I^2 <25%, the heterogeneity is assessed as evidence of low; as moderate if 25% ≤ I^2 ≤ 50%; as high if I^2 >25%.[33] When the heterogeneity is low, the fix effect model will be used; otherwise, a random effect model will be used. In addition, we will also evaluate the transitivity and inconsistency of NMA, respectively. The transitivity will be assessed by use of descriptive statistics for study types and demographic characteristics. Both fixed and random effects models will be run. Inconsistency will be assessed by comparing deviation information criteria (DIC) statistics in the fitted consistency and inconsistency models.[34] Global inconsistency between direct and indirect comparisons will also be evaluated by using a loop-specific method, if a loop connecting three or more arms exists.[35]

Subgroup analysis

We will explore whether a particular subtypes of breast cancer might be more appropriate for specific duration treatments with trastuzumab.

We still stratify breast cancer into the following groups when possible: Estrogen Receptor (ER) positive, ER negative, node positive and node negative. The subgroup analyses will be conducted regardless of heterogeneity estimates.

Sensitivity analysis

We will plan sensitivity analyses to assess the robustness and reliability of findings in our NMA. In order to check the impact of HER2 status on the results, the first analysis will exclude patients with HER2 negative after re-evaluating the HER2 status in the E2198 trial.[36] The second sensitivity analysis will restrict hormone receptor-positive (ER + and PR +, ER + and PR -, ER - and PR+). Lastly, the sensitivity analysis will stratify patients as 1-3 and ≥4 positive lymph nodes to observe the impact of the number of positive lymph node.

Discussion

Despite highly effective in treatment with trastuzumab for HER2-positive early breast cancer, substantial socio-economic burden and cardiotoxicity attracted the attention of governments, academic researchers, pharmaceutical companies and health care payers. The trade-offs between efficacy and cardiotoxicity were considerable. Most clinicians deemed that 83% four-year DFS with six months trastuzumab is acceptable.[37]This benefit-risk analysis is important information to help clinicians and patients choose optimum duration of adjuvant treatment

with trastuzumab in their daily practice.

The 12 months of treatments with trastuzumab for most women with early HER2 positive breast cancer was standard of care, but most crucial RCTs mainly focused on patients with high-risk of recurrence and the 1-year duration was chosen arbitrarily. In contrary, a particular subtype of patients might be appropriate for de-escalating duration treatment, without compromise of their efficacy. Romualdo and his colleagues deemed that de-escalating chemotherapy was candidate for older and stages I HER2-positive breast cancer.[38] This study will explore whether de-escalating targeted therapy is another option of for patients with particular subtypes (ER positive and node negative).

As far as we know, the results of system review will fill a pivital knowledge gap of optimal duration of adjuvant trastuzumab in patients with early HER2 positive breast cancer. We hope the findings from this NMA will help clinicians and patients select optimal duration of adjuvant trastuzumab with the greatest value in HER2 positive early breast cancers. Additionally, currently under-recognized comparisons (e.g., 6 months vs 9 weeks) may be identified by this Bayesian analysis to guide future researches.

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Author contributions

QcH and DC conceptualized the network meta-analysis. QcH and XW co-developed the search strategy. Both QcH and XW were major contributors in writing the manuscript. The protocol was revised by DC, YC, XfL and TL. DC and TL were serving as guarantor and corresponding author of this study. All authors approved the final manuscript and agreed to submit the protocol in the journal.

Ethics approval and dissemination

Ethics review boards is not required for this network meta-analysis. The results will be disseminated through international conference reports and

peer-reviewed manuscripts.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and stated that there is no organization to support the submission; no organization is interested in the submitted work; no other relationships or activities effect the submitted work.

Provenance and peer review

Not commissioned; externally peer reviewed

Patient and public involvement

No patient involvement.

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A sample Pubmed search strategy was as follows:

#1 Breast Neoplasm [MeSH Terms]

#2 breast neoplasm [title/abstract]

#3 neoplasm, breast [title/abstract]

#4 breast tumors [title/abstract]

#5 breast tumor [title/abstract]

#6 tumor, breast [title/abstract]

#7 tumors, breast [title/abstract]

#8 neoplasms, breast [title/abstract]

#9 breast cancer [title/abstract]

#10 cancer, breast [title/abstract]

#11 mammary cancer [title/abstract]

#12 cancer, mammary [title/abstract]

#13 cancers, mammary [title/abstract]

#14 mammary cancers [title/abstract]

#15 malignant neoplasm of breast [title/abstract]

#16 breast malignant neoplasm [title/abstract]

#17 breast malignant neoplasms [title/abstract]

#18 malignant tumor of breast [title/abstract]

#19 breast malignant tumor [title/abstract]

#20 cancer of breast [title/abstract]

#21 cancer of the breast [title/abstract]

#22 mammary carcinoma, human [title/abstract]

#23 carcinoma, human mammary [title/abstract]

#24 carcinomas, human mammary [title/abstract]

#25 human mammary carcinomas [title/abstract]

#26 mammary carcinomas, human [title/abstract]

#27 human mammary carcinoma [title/abstract]

#28 mammary neoplasms, human [title/abstract]

#29 human mammary neoplasms [title/abstract]

#30 human mammary neoplasms [title/abstract]

#31 neoplasm, human mammary [title/abstract]

#32 neoplasms, human mammary [title/abstract]

#33 mammary neoplasm, human [title/abstract]

#34 breast carcinoma [title/abstract]

#35 breast carcinomas [title/abstract]

#36 carcinoma, breast [title/abstract]

#37 carcinomas, breast [title/abstract]

#38 breast malignant tumors [title/abstract]

#39 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38

#40 Genes, erbB-2[MeSH Terms]

#41 c-erbB-2 Genes[Title/Abstract]

#42 c erbB 2 Genes[Title/Abstract]

#43 c-erbB-2 Gene[Title/Abstract]

#44 Genes, erbb2[Title/Abstract]

#45 Gene, erbb2[Title/Abstract]

#46 erbb2 Gene[Title/Abstract]

#47 erbb2 Genes[Title/Abstract]

#48 Genes, HER-2[Title/Abstract]

#49 HER-2 Gene[Title/Abstract]

#50 HER-2 Genes[Title/Abstract]

#51 Genes, neu[Title/Abstract]

#52 neu Gene[Title/Abstract]

#53 neu Genes[Title/Abstract]

#54 Genes, HER2[Title/Abstract]

#55 Gene, HER2[Title/Abstract]

#56 HER2 Gene[Title/Abstract]

#57 HER2 Genes[Title/Abstract]

#58 erbB-2 Genes[Title/Abstract]

#59 erbB 2 Genes[Title/Abstract]

#60 erbB-2 Gene[Title/Abstract]

#61 c-erbB-2 Proto-Oncogenes[Title/Abstract]

#62 c erbB 2 Proto Oncogenes[Title/Abstract]

#63 c-erbB-2 Proto-Oncogene[Title/Abstract]

#64 #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63

#65 Trastuzumab[MeSH Terms]

#66 Herceptin[Title/Abstract]

#67 #65 OR #66

#68 #39 AND #64 AND #67

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Optimum duration of adjuvant trastuzumab in treatment of human epidermal growth factor receptor-2 positive early breast cancer: protocol for a network meta-analysis of randomized trials

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Abstract

Introduction: Controversy regarding optimum duration of trastuzumab treatment remains in patients with human epidermal growth factor receptor-2 (HER2) positive early breast cancer. The objective of applying network meta-analysis (NMA) is to integrate existing evidence based on direct and indirect comparisons of efficacy and safety, and then to determine the duration of trastuzumab treatments with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.

Methods and analysis: Electronic searching of trastuzumab treatments for early breast cancers by titles/abstracts will be conducted for the period from inception to June 16, 2019 using PubMed, Cochrane Library, Embase and ClinicalTrils.gov, as well as the annual meetings of San Antonio Breast Cancer Symposium (SABCS), European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) online archives. The outcomes of interest are overall survival, disease-free survival, acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities. Two independent reviewers will screen and extract eligible data based on the inclusion and exclusion criteria, and then assess the risk of bias and evidence quality of individual studies using Cochrane Collaboration's tool and GRADE (Grades of Recommendation, Assessment, Development and Evaluation). The heterogeneity, transitivity and inconsistency of NMA will be evaluated.

We will also perform subgroup and sensitivity analyses to assess the robustness and reliability of findings in our NMA.

Ethics and dissemination: Ethics approval is not required for our NMA. This study will identify the evidence regarding optimum duration of trastuzumab treatment in patients with HER2 positive early breast cancer. We hope the findings from our study will help clinicians, patients and policy makers to reduce the uncertainty of escalating and de-escalating duration treatment and to select optimum duration of trastuzumab treatment with the highest efficacy and safety. Findings from our NMA will be submitted to peer-reviewed journal and international conference reports.

Strengths and limitations of this study

- Our objective of applying NMA is to integrate existing evidence based on direct and indirect comparisons of efficacy and safety, and to determine the duration of trastuzumab treatments with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.
- Our study findings will help clinicians, patients and policy makers to reduce the uncertainty of escalating and de-escalating duration treatment and to select optimum duration of trastuzumab treatment with highest efficacy and safety.

- We will perform subgroup and sensitivity analyses to assess the robustness and reliability of NMA results.
- Language bias is the potential limitation of our study as NMA will only include published studies in English.

Trial registration number CRD42019139109

Keywords: early breast cancer, human epidermal growth factor receptor-2, trastuzumab, network meta-analysis, protocol

Introduction

Human epidermal growth factor receptor-2 (HER2) positive breast cancer accounts for approximately 20–25% of overall reported cases(1,2) and is associated with poor prognosis.(3,4) Trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 protein, is used for patients with HER2-positive early breast cancer. (5-7) Recently, targeted therapy using one year of trastuzumab has been proven to improve overall survival (OS) and disease-free survival (DFS) significant in early HER2-positive breast cancer. (8-12)

However, the optimal duration of trastuzumab treatment has been an intense controversy and ongoing debate in terms of efficacy, toxicity, convenience and cost.(13) High-quality randomised controlled trials (RCTs) has confirmed that multiple treatment durations of trastuzumab were effective for HER2-positive early breast cancers, but the relative efficacy and safety were not evaluated for all head-to-head trials. More specifically, the HERceptin Adjuvant (HERA) trial has confirmed that 24 months of adjuvant trastuzumab, which was associated with a higher cost and cardiac toxicity, would not improve DFS compared to 12 months of adjuvant therapy [hazard ratio (HR) 1.02, 95% confidence intervals (CI) 0.89–1.17], at a higher cost, inconvenience and cardiac toxicity (7.3% vs 4.4%). (14) While comparing to the 12 months of trastuzumab treatment,

six months of trastuzumab treatment was non-inferior and associated with decreased cardiac toxicity (8% vs 4%, P<0.001) in the PERSEPHONE trial, but was not non-inferior in the PHARE and HORG trials(15-17). In contrast, the SOLD and Short-HER trials applying nine weeks of trastuzumab was not non-inferior compared to the 12 months of trastuzumab, and a significant reduction in cardiac toxicity was observed in nine weeks of trastuzumab. (18,19)

Direct comparison among preventive strategies was limited as half of RCTs, including N9831, NSABP-B31, BCIRG 006 and FinHER trials, were comparing active therapy to inactive interventions (e.g., placebo). (10,11,20) Pivotal pairwise meta-analyses have been used to evaluate the efficacy and toxicity between shorter durations of trastuzumab and standard option directly. The analyses results suggested that 12 months of trastuzumab would still be the optimal treatment for early HER2-positive breast cancer, albeit with a significant increase in cardiac events. (13,21-24)

These intriguing results provoked a heated debate about whether should consider escalating and de-escalating duration treatment as new standard of care. Network meta-analysis (NMA) will provide indirect evaluations on the relative efficacy and toxicity of multiple durations of adjuvant trastuzumab therapies in HER2-positive early breast cancer. (25) To address the aforementioned debate and determine the most

appropriate treatment options, we will conduct NMA to integrate existing evidence available, based on direct and indirect comparisons of efficacy and safety, and to determine the duration of trastuzumab treatments (24 months vs 12 months vs 6 months vs 12weeks vs 9 weeks vs placebo/observation/zero) with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.

Methods

The results of our protocol will be evaluated in line with the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols).(26) Similarly, we will perform NMA in guidance of the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions. (27) This project has been registered in PROSPERO (CRD42019139109).

Search strategy

Electronic searching by titles/abstracts of trastuzumab treatments for early breast cancers will be performed using PubMed, Cochrane Library, Embase (Ovid interface) and ClinicalTrials.gov, as well as the annual meetings of San Antonio Breast Cancer Symposium (SABCS) (2015-2019), European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) online archives until June 16, 2019. Two reviewers who have been trained in data extraction

will conduct search strategies independently. The same two authors will search reference lists manually from eligible reviews and relevant trials to identify additional potential papers. We will record the reason of excluding the full text and generate a PRISMA flow diagram for the NMA. (28)

The terms used for literature searching will include the following domains of Medical Subject Heading (MeSH) terms: 'breast cancer', 'human epidermal growth factor receptor-2' and 'trastuzumab', according to PICOS (Population Intervention Comparison Outcomes Study Design) statement. MeSH and Subheadings will be combined with 'AND' or 'OR'. The complete search strategy is presented in online supplementary file 1 (see the appendix 1).

We will perform a pilot test to evaluate inter-rater reliability and adjust each screening stage: title and abstract, followed by full-text screening. Two independent reviewers will screen the titles/abstracts of related studies based on inclusion and exclusion criteria. The eligible or potentially eligible trials will be evaluated by reading through the full texts when necessary. Moreover, disagreements in data extraction will be discussed with the help of the third reviewer.

Eligibility criteria

Trials will be eligible if they adhere to the following criteria: 1. Populations: patients with HER2-positive early breast cancer of any age

or nationality were treated with trastuzumab treatments; 2. Interventions: any duration of trastuzumab treatments were given. We are also interested in the impact of placebo/observation/zero as adjuvant treatment; 3. Comparators: 12 months of trastuzumab treatment was compared with placebo/observation/zero, or other durations of adjuvant trastuzumab; 4. Outcomes: OS, DFS, acceptability, and cardiotoxicities and grade 3-4 nonhematologic toxicities; 5. Study design: RCTs that compared any two or more different arms of adjuvant trastuzumab in patients with HER2-positive early breast cancer; 6. Language and other limitations: We will include studies published in English regardless of publication status.

Studies not meeting the inclusion criteria will be excluded. The other excluding criteria are as follows: 1. Neoadjuvant and adjuvant treatment with trastuzumab biosimilars; 2. Palliative care with trastuzumab; 3. Non-randomised studies, such as prospective cohort studies.

Outcomes

The outcomes of interest are OS (defined as the time from randomization to death from any cause), DFS (defined as the time from randomization to local, regional, distant relapse, contralateral breast cancer, second primary cancer, or death from any cause, whichever occurred first), acceptability (defined as the proportion of patients who discontinued trastuzumab), cardiotoxicities, and grade 3-4 nonhematologic toxicities. The cardiac toxicity grading is used by the

Common Terminology Criteria for Adverse Events of the National Cancer Institute. Cardiac toxicity is defined as an asymptomatic decline in left ventricular ejection fraction (LVEF) to ≤45%, an absolute drop of 10-15% in follow-up echocardiography, symptomatic congestive heart failure (New York Heart Association [NYHA] class III/IV) or cardiac death.(29,30) We will calculate the relative effectiveness for each network comparison among all duration of treatments with trastuzumab. (31)

Data extraction and management

The management of literature searching records will be carried out in EndNote X7. A spreadsheet will be created in Microsoft Excel 2010 (Microsoft Corp, Redmond, WA, www.microsoft.com) to collect outcomes of interest, such as study ID, first author, study design, recruitment time frame, detailed interventions, sample size, and endpoints (OS, DFS, acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities). We will contact corresponding authors and relevant pharmaceutical companies if important data are not reported. If duplicate publications are identified, the most up-to-date data will be included.

Bias risk

The risk of bias of RCTs in the NMA will be evaluated by reviewer manager according to the following domains outlined in the Cochrane Collaboration's tool: random sequence generation, allocation

concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias(32). Two authors will review RCTs independently and report a high risk of bias as "-", a low risk of bias as "+", or an unclear risk of bias as "?". Any disagreements in assessment of risk of bias will be resolved by discussion, or the help of the third reviewer if needed.

Quality of evidence

We will evaluate the quality of evidence of individual studies using GRADE (Grades of Recommendation, Assessment, Development and Evaluation), which is based on the following five domains: risk of bias, imprecision, inconsistency, indirectness and publication bias(33,34). The staging system categories for GRADE evidences are scored as high, moderate, low or very low quality. The initial confidence level for each RCT is set as high, but will be rated down based on the evaluation of the five domains. The strength of evidences will also be graded for the outcomes based on GRADE system in CINeMA. (34)

Statistical analysis

We will perform the traditional pairwise meta-analysis on direct comparisons based on two or more studies with Stata13.0 (StataCorp, College Station, TX, USA). To compare eligible interventions directly and indirectly, NMA displaying outcomes of interest is planned using

WinBUGS version1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

Pooled hazard ratios (HRs) for OS and DFS with 95% confidence intervals (CIs) will be calculated using both fixed- and random-effects model. Binary outcomes (acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities) are expressed as odds ratios (ORs) with 95% CI. The results of comparative effectiveness and safety probability statements of intervention effects will be ranked; and rank plots across all outcomes will be generated. The interventions with surface under the cumulative ranking (SUCRA) in term of efficacy and safety will be evaluated to interpret relative effect of comparisons. We will compare the risk-benefit profile of all comparators in terms of efficacy and toxicity. Two sided $p< 0.05$ is considered significant.

We will estimate the presence of heterogeneity based on the magnitude of I^2 estimated from pairwise meta-analysis models. If I^2 <25%, the heterogeneity is considered as evidence of low; as moderate if $25\% \leq I^2 \leq 50\%$; as high if I^2 >25%. (35) The fixed- effects model will be used when the heterogeneity is low; otherwise, a random- effects model will be used. In addition, we will also evaluate the transitivity and inconsistency of NMA. The transitivity will be assessed by using/applying descriptive statistics for study types and demographic characteristics. Inconsistency will be assessed by comparing deviation information criteria (DIC) statistics in the fitted consistency and inconsistency models. (36) Global

inconsistency between direct and indirect comparisons will also be evaluated by using a loop-specific method, if a loop connecting three or more arms exists. (37)

Subgroup analysis

We will explore whether specific duration treatments with trastuzumab might be more appropriate for particular subtypes of breast cancer. We categorize breast cancer into the following groups when possible: Estrogen Receptor (ER) positive, ER negative, node positive and node negative.

Sensitivity analysis

We will perform sensitivity analyses to assess the robustness and reliability of findings in our NMA. In order to check the impact of HER2 status on the results, the first sensitivity analysis will exclude patients with HER2 negative after re-evaluating the HER2 status in the E2198 trial. (38) The second sensitivity analysis will restrict hormone receptor-positive to ER + and PR +, ER + and PR -, ER - and PR + . Lastly, the sensitivity analysis will classify patients as 1-3 and ≥4 positive lymph nodes to specify the impact of the number of positive lymph nodes.

Ethics and dissemination

Ethics approval is not required for our NMA. Despite trastuzumab being highly effective in treatment for HER2-positive early breast cancer,

its substantial socio-economic burden attracted the attention of governments, academic researchers, pharmaceutical companies and health care payers. With the consideration of balancing efficacy and cardiotoxicity, the 12-month and 6-month of durations of trastuzumab treatments have received increasing interests. The perspective of balancing efficacy and cardiotoxicity were heightened interest in 12-month and 6-month of durations of trastuzumab treatments. Compared to the 12-month durations of trastuzumab treatments, most clinicians suggested that a drop to 83% four-year DFS with six months trastuzumab would be also acceptable. (39) This benefit-risk analysis will provide important information to help clinicians, patients and policy makers to choose optimum duration of adjuvant treatment with trastuzumab in their daily practice.

The 12 months of treatments with trastuzumab for most women with early HER2 positive breast cancer was standard of care, but the most crucial RCTs mainly focused on patients with high-risk of recurrence and the 1-year duration was chosen arbitrarily. In contrary, a particular subtype of patients might be appropriate for de-escalating duration of treatment, without compromising efficacy. Romualdo and his colleagues deemed that de-escalating chemotherapy was a good candidate for older patients and those with stage I HER2-positive breast cancer. (40) This study will explore whether de-escalating targeted therapy is another

option for patients with particular subtypes (ER positive and node negative).

As far as we know, the results of system review will fill a pivotal knowledge gap of optimal duration of adjuvant trastuzumab in patients with early HER2 positive breast cancer. We hope the findings from this NMA will help clinicians, patients and policy makers to select optimal duration of adjuvant trastuzumab with the greatest value in HER2 positive early breast cancers. It will also provide a result that will engage patients and policy makers and contribute to the public debate about future policy options. In addition, results from this academic study will facilitate the discussion on the future policy options between patients and policy makers. Furthermore, currently under-recognized comparisons (e.g., 6 months vs 9 weeks) may be identified by this Bayesian analysis to guide future research.

Patient and public involvement

The manuscript was developed without patient or public participation.

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Author contributions

QcH and DC conceptualized the network meta-analysis. QcH and XW co-developed the search strategy. Both QcH and XW were major contributors in writing the manuscript. The protocol was revised by DC, YC, XfL and TL. DC and TL were serving as guarantor and corresponding author of this study. All authors approved the final

manuscript and agreed to submit the protocol in the journal.

Ethics approval and dissemination

Ethics review boards is not required for this network meta-analysis. The results will be disseminated through international conference reports and peer-reviewed manuscripts.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and stated that there is no organization to support the submission; no organization is interested in the submitted work; no other relationships or activities effect the submitted work.

Provenance and peer review

Not commissioned; externally peer reviewed

Patient consent for publication

Not required.

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A sample Pubmed search strategy was as follows:

#1 Breast Neoplasm [MeSH Terms]

#2 breast neoplasm [title/abstract]

#3 neoplasm, breast [title/abstract]

#4 breast tumors [title/abstract]

#5 breast tumor [title/abstract]

#6 tumor, breast [title/abstract]

#7 tumors, breast [title/abstract]

#8 neoplasms, breast [title/abstract]

#9 breast cancer [title/abstract]

#10 cancer, breast [title/abstract]

#11 mammary cancer [title/abstract]

#12 cancer, mammary [title/abstract]

#13 cancers, mammary [title/abstract]

#14 mammary cancers [title/abstract]

#15 malignant neoplasm of breast [title/abstract]

#16 breast malignant neoplasm [title/abstract]

#17 breast malignant neoplasms [title/abstract]

#18 malignant tumor of breast [title/abstract]

#19 breast malignant tumor [title/abstract]

#20 cancer of breast [title/abstract]

#21 cancer of the breast [title/abstract]

#22 mammary carcinoma, human [title/abstract]

#23 carcinoma, human mammary [title/abstract]

#24 carcinomas, human mammary [title/abstract]

#25 human mammary carcinomas [title/abstract]

#26 mammary carcinomas, human [title/abstract]

#27 human mammary carcinoma [title/abstract]

#28 mammary neoplasms, human [title/abstract]

#29 human mammary neoplasms [title/abstract]

#30 human mammary neoplasms [title/abstract]

#31 neoplasm, human mammary [title/abstract]

#32 neoplasms, human mammary [title/abstract]

#33 mammary neoplasm, human [title/abstract]

#34 breast carcinoma [title/abstract]

#35 breast carcinomas [title/abstract]

#36 carcinoma, breast [title/abstract]

#37 carcinomas, breast [title/abstract]

#38 breast malignant tumors [title/abstract]

#39 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38

#40 Genes, erbB-2[MeSH Terms]

#41 c-erbB-2 Genes[Title/Abstract]

#42 c erbB 2 Genes[Title/Abstract]

#43 c-erbB-2 Gene[Title/Abstract]

#44 Genes, erbb2[Title/Abstract]

#45 Gene, erbb2[Title/Abstract]

#46 erbb2 Gene[Title/Abstract]

#47 erbb2 Genes[Title/Abstract]

#48 Genes, HER-2[Title/Abstract]

#49 HER-2 Gene[Title/Abstract]

#50 HER-2 Genes[Title/Abstract]

#51 Genes, neu[Title/Abstract]

#52 neu Gene[Title/Abstract]

#53 neu Genes[Title/Abstract]

#54 Genes, HER2[Title/Abstract]

#55 Gene, HER2[Title/Abstract]

#56 HER2 Gene[Title/Abstract]

#57 HER2 Genes[Title/Abstract]

#58 erbB-2 Genes[Title/Abstract]

#59 erbB 2 Genes[Title/Abstract]

#60 erbB-2 Gene[Title/Abstract]

#61 c-erbB-2 Proto-Oncogenes[Title/Abstract]

#62 c erbB 2 Proto Oncogenes[Title/Abstract]

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#64 #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63

#65 Trastuzumab[MeSH Terms]

#66 Herceptin[Title/Abstract]

#67 #65 OR #66

#68 #39 AND #64 AND #67

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	16
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-8, supplementary

			file
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11-12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Optimum duration of adjuvant trastuzumab in treatment of human epidermal growth factor receptor-2 positive early breast cancer: protocol for a network meta-analysis of randomized controlled trials

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Optimum duration of adjuvant trastuzumab in treatment of human epidermal growth factor receptor-2 positive early breast cancer: protocol for a network meta-analysis of randomized controlled trials

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Abstract

Introduction: Controversy regarding optimum duration of trastuzumab treatment remains in patients with human epidermal growth factor receptor-2 (HER2) positive early breast cancer. The objective of applying network meta-analysis (NMA) is to integrate existing evidence based on direct and indirect comparisons of efficacy and safety, and then to determine the duration of trastuzumab treatments with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.

Methods and analysis: Electronic searching of trastuzumab treatments for early breast cancer by titles and abstracts will be conducted for the period from inception to June 16, 2019 using PubMed, Cochrane Library, Embase and ClinicalTrils.gov, as well as the annual meetings of San Antonio Breast Cancer Symposium (SABCS), European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) online archives. The outcomes of interest are overall survival, disease-free survival, acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities. Two independent reviewers will screen and extract eligible data based on the inclusion and exclusion criteria, and then assess the risk of bias and evidence quality of individual studies using Cochrane Collaboration's tool and Grades of Recommendation, Assessment, Development and Evaluation (GRADE). The heterogeneity, transitivity and inconsistency of NMA will be evaluated. In addition, we

will perform subgroup and sensitivity analyses to assess the robustness and reliability of findings in our NMA.

Ethics and dissemination: Ethics approval is not required for our NMA. This study will identify the evidence regarding optimum duration of trastuzumab treatment in patients with HER2 positive early breast cancer. Findings from our NMA will be submitted as peer-reviewed journal manuscripts and international conference reports.

Strengths and limitations of this study

- Our objective of applying NMA is to integrate existing evidence based on direct and indirect comparisons of efficacy and safety, and to determine the duration of trastuzumab treatments with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.
- Our study findings will help clinicians, patients and policy makers to reduce the uncertainty of escalating and de-escalating duration treatment and to select the optimum duration of trastuzumab treatment with highest efficacy and safety.
- We will perform subgroup and sensitivity analyses to assess the robustness and reliability of NMA results.
- Language bias is the potential limitation of our study as NMA will only include published studies in English.

Trial registration number CRD42019139109

Keywords: early breast cancer, human epidermal growth factor receptor-2, trastuzumab, network meta-analysis, protocol

Introduction

Human epidermal growth factor receptor-2 (HER2) positive breast cancer accounts for approximately 20–25% of overall reported cases(1,2) and is associated with poor prognosis.(3,4) Trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 protein, is used for patients with HER2-positive early breast cancer. (5-7) Recently, targeted therapy using one year of trastuzumab has been proven to improve overall survival (OS) and disease-free survival (DFS) significantly in early HER2-positive breast cancer. (8-11) Compared to treatment using chemotherapy only in early HER2-positive breast cancer, treatment using adjuvant trastuzumab plus chemotherapy tends to reduce the risk of recurrence and death by one-third. (12)

However, the optimal duration of trastuzumab treatment has been an intense controversy and ongoing debate in terms of efficacy, toxicity, convenience and cost.(13) High-quality randomized controlled trials (RCTs) have confirmed that multiple treatment durations of trastuzumab were effective for HER2-positive early breast cancers, but the relative efficacy and safety were not evaluated for all head-to-head trials. More specifically, the HERceptin Adjuvant (HERA) trial has confirmed that 24 months of adjuvant trastuzumab treatment, which was associated with a higher cost, inconvenience and cardiac toxicity (7.3% vs 4.4%), would

not improve DFS compared to a 12 months of adjuvant therapy treatment [hazard ratio (HR) 1.02, 95% confidence intervals (CI) 0.89–1.17]. (14) While comparing to the 12 months of trastuzumab treatment, six months of trastuzumab treatment was non-inferior and associated with decreased cardiac toxicity (8% vs 4%, $P<0.001$) in the PERSEPHONE trial, but was not non-inferior in the PHARE and HORG trials.(15-17) In contrast, the SOLD and Short-HER trials applying nine weeks of trastuzumab was not non-inferior compared to the 12 months of trastuzumab, and a significant reduction in cardiac toxicity was observed in nine weeks of trastuzumab. (18,19)

Direct comparison among preventive strategies was limited, as half of RCTs, including N9831, NSABP-B31, BCIRG 006 and FinHER trials, comparing active therapy to inactive interventions (e.g., placebo). (10,11,20) Pivotal pairwise meta-analyses have been used to evaluate the efficacy and toxicity between shorter durations of trastuzumab and standard option directly. The analyses results suggested that 12 months of trastuzumab would still be the optimal treatment for early HER2-positive breast cancer, albeit with a significant increase in cardiac events. (13,21-24)

These intriguing results provoked an intense debate on consideration escalating and de-escalating duration treatment as new standard of care. Network meta-analysis (NMA) will provide indirect evaluations on the

relative efficacy and toxicity of multiple durations of adjuvant trastuzumab therapies in HER2-positive early breast cancer. (25) To address the aforementioned debate and determine the most appropriate treatment options, we will conduct NMA to integrate existing evidence available, based on direct and indirect comparisons of efficacy and safety, and to determine the duration of trastuzumab treatments (24 months vs 12 months vs six months vs 12weeks vs nine weeks vs placebo/observation/zero) with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.

Methods

The results of our protocol will be evaluated in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P).(26) Similarly, we will perform NMA in guidance of the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions. (27) This project has been registered in PROSPERO (CRD42019139109).

Search strategy

Electronic searching by titles and abstracts of trastuzumab treatments for early breast cancers will be performed using PubMed, Cochrane Library, Embase (Ovid interface) and ClinicalTrials.gov, as well as the annual meetings of San Antonio Breast Cancer Symposium (SABCS) (2015-2019), European Society of Medical Oncology (ESMO) and

American Society of Clinical Oncology (ASCO) online archives until June 16, 2019. Two reviewers who have been trained in data extraction will conduct search strategies independently. The same two authors will search reference lists manually from eligible reviews and relevant trials to identify additional potential papers. We will record the reasons of excluding the full text and generate a PRISMA flow diagram for the NMA. (28)

The terms used for literature searching will include the following domains of Medical Subject Heading (MeSH) terms: 'breast cancer', 'human epidermal growth factor receptor-2' and 'trastuzumab', according to Population Intervention Comparison Outcomes Study Design (PICOS) statement. MeSH and Subheadings will be combined with 'AND' or 'OR'. The complete search strategy is presented in online supplementary file 1 (see the appendix 1).

We will perform a pilot test to evaluate inter-rater reliability and adjust each screening stage: title and abstract, followed by full-text screening. Two independent reviewers will screen the titles and abstracts of related studies based on inclusion and exclusion criteria. The eligible or potentially eligible trials will be evaluated by reading through the full texts when necessary. Moreover, disagreements in data extraction will be discussed with the help of the third reviewer.

Eligibility criteria

Trials will be eligible if they fulfill the following criteria: 1. Populations: patients with HER2-positive early breast cancer of any age or nationality were treated with trastuzumab treatments; 2. Interventions: any duration of trastuzumab treatments were given. We are also interested in the impact of placebo/observation/zero as adjuvant treatment; 3. Comparators: 12 months of trastuzumab treatment was compared with placebo/observation/zero, or other durations of adjuvant trastuzumab; 4. Outcomes: OS, DFS, acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities; 5. Study design: RCTs that compared any two or more different arms of adjuvant trastuzumab in patients with HER2-positive early breast cancer; 6. Language and other limitations: We will include studies published in English regardless of publication status.

Studies not meeting the inclusion criteria will be excluded. The other excluding criteria are as follows: 1. Neoadjuvant and adjuvant treatment with trastuzumab biosimilars; 2. Palliative care with trastuzumab.

Outcomes

The outcomes of interest are OS (defined as the time from randomization to death from any cause), DFS (defined as the time from randomization to local, regional, distant relapse, contralateral breast cancer, second primary cancer, or death from any cause, whichever occurred first), acceptability (defined as the proportion of patients who discontinued trastuzumab), cardiotoxicities, and grade 3-4

nonhematologic toxicities. The cardiac toxicity grading is used by the Common Terminology Criteria for Adverse Events of the National Cancer Institute. Cardiac toxicity is defined as an asymptomatic decline in left ventricular ejection fraction (LVEF) to ≤45%, an absolute drop of 10-15% in follow-up echocardiography, symptomatic congestive heart failure (New York Heart Association [NYHA] class III/IV) or cardiac death.(29,30) We will calculate the relative effectiveness for each network comparison among all duration of treatments with trastuzumab. (31)

Data extraction and management

The management of literature searching records will be carried out in EndNote X7. A spreadsheet will be created in Microsoft Excel 2010 (Microsoft Corp, Redmond, WA, www.microsoft.com) to collect outcomes of interest, such as study ID, first author, study design, recruitment time frame, detailed interventions, sample size, and endpoints (OS, DFS, acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities). We will contact corresponding authors and relevant pharmaceutical companies for further information if important data are not reported in articles. The most up-to-date data will be included if duplicate publications are identified.

Bias risk

The risk of bias of RCTs in the NMA will be evaluated by reviewer

manager according to the following domains outlined in the Cochrane Collaboration's tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.(32) Two authors will review RCTs independently and report a high risk of bias as "-", a low risk of bias as "+", or an unclear risk of bias as "?". Any disagreements in assessment of risk of bias will be resolved by discussion, or the help of the third reviewer if needed.

Quality of evidence

We will evaluate the quality of evidence of individual studies using Grades of Recommendation, Assessment, Development and Evaluation (GRADE), which is based on the following five domains: risk of bias, imprecision, inconsistency, indirectness and publication bias.(33,34) The staging system categories for GRADE evidences are scored as high, moderate, low or very low quality. The initial confidence level for each RCT is set as high, but will be rated down based on the evaluation of the five domains. The strength of evidences will also be graded for the outcomes based on GRADE system in CINeMA. (34)

Statistical analysis

We will perform the traditional pairwise meta-analysis on direct comparisons based on two or more studies with Stata13.0 (StataCorp,

College Station, TX, USA). To compare eligible interventions directly and indirectly, NMA displaying outcomes of interest is planned using WinBUGS version1.4.3 (MRC Biostatistics Unit, Cambridge, UK). Pooled hazard ratios (HRs) for OS and DFS with 95% confidence intervals (CIs) will be calculated using both fixed- and random-effects models. Binary outcomes (acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities) are expressed as odds ratios (ORs) with 95% CI. The results of comparative effectiveness and safety probability statements of intervention effects will be ranked; and rank plots across all outcomes will be generated. The interventions with surface under the cumulative ranking (SUCRA) in term of efficacy and safety will be evaluated to interpret relative effect of comparisons. We will compare the risk-benefit profile of all comparators in terms of efficacy and toxicity. A two-sided $p< 0.05$ is considered statistically significant.

We will estimate the presence of heterogeneity based on the magnitude of I^2 estimated from pairwise meta-analysis models. The heterogeneity is considered as evidence of low if $I^2 <25\%$, as moderate if $25\% \leq I^2 \leq 50\%$, and as high if $I^2 >50\%$. (35) The fixed-effects model will be used when the heterogeneity is low and moderate; otherwise, a random-effects model will be used. In addition, we will also evaluate the transitivity and inconsistency of NMA. The transitivity will be assessed by applying

descriptive statistics for study types and demographic characteristics. Inconsistency will be assessed by comparing deviation information criteria (DIC) statistics in the fitted consistency and inconsistency models. (36) Global inconsistency between direct and indirect comparisons will also be evaluated by using a loop-specific method, if a loop connecting three or more arms exists. (37)

Subgroup analysis

We will explore whether specific duration of treatments with trastuzumab might be more appropriate for particular subtypes of breast cancer. We categorize breast cancer into the following groups when possible: Estrogen Receptor (ER) positive, ER negative, node positive and node negative.

Sensitivity analysis

We will perform sensitivity analyses to assess the robustness and reliability of findings in our NMA. In order to check the impact of HER2 status on the results, the first sensitivity analysis will exclude patients with HER2 negative after re-evaluating the HER2 status in the E2198 trial. (38) The second sensitivity analysis will restrict hormone receptor-positive to ER + and PR +, ER + and PR -, ER - and PR +. Lastly, the sensitivity analysis will classify patients as 1-3 and ≥4 positive lymph nodes to specify the impact of the number of positive lymph nodes.

Ethics and dissemination

An ethics approval is not required for the NMA. Important modifications to the study protocol will be communicated to all members of the research team. The results will be disseminated through international conference reports and published in a peer-reviewed journal.

Discussion

Despite trastuzumab being highly effective in treatment for HER2-positive early breast cancer, its substantial socio-economic burden attracted the attention of governments, academic researchers, pharmaceutical companies and health care payers. With the consideration of balancing efficacy and cardiotoxicity, the 12-month and six-month of trastuzumab treatments have received increasing interests. The requirement to balance efficacy and side effects (i.e. cardiotoxicity) has led to raise interest in reducing trastuzumab duration from 12 months to six months. With the increase in rates of patients reporting 12-month trastuzumab induced cardiotoxicity, most clinicians suggested that a drop to 83% four-year DFS with six months trastuzumab would be also acceptable. (39) This benefit-risk analysis will provide important information to help clinicians, patients and policy makers to decide optimum duration of adjuvant treatment with trastuzumab in their daily practice.

The 12 months of treatments with trastuzumab for most women with

early HER2 positive breast cancer was a standard of care, but most crucial RCTs mainly focused on patients with high-risk of recurrence and one-year duration was chosen arbitrarily. In contrary, a particular subtype of patients might be appropriate for de-escalating duration of treatment, without compromising efficacy. Romualdo and his colleagues deemed that de-escalating chemotherapy was a good option for older patients and those with stage I HER2-positive breast cancer. (40) This study will explore whether de-escalating targeted therapy is another option for patients with particular subtypes (ER positive and node negative).

As far as we know, the results of system review will fill a pivotal knowledge gap of optimal duration of adjuvant trastuzumab in patients with early HER2 positive breast cancer. We hope the findings from this NMA will help clinicians, patients and policy makers to select optimal duration of adjuvant trastuzumab with the greatest value in HER2 positive early breast cancers. It will also provide a result that will engage patients and policy makers, and will contribute to the public debate on future policy options. Furthermore, under-recognized comparisons (e.g., six months vs nine weeks) may be identified by this Bayesian analysis to guide future research.

Patient and public involvement

The manuscript was developed without patient or public participation. Breast cancer patient organizations will participate in the discussion and

dissemination of research results. A summary of the findings will be provided to the Chinese society of clinical oncology (CSCO).

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Author contributions

QcH and DC conceptualized the network meta-analysis. QcH and XW co-developed the search strategy. Both QcH and XW were major contributors in writing the manuscript. The protocol was revised by DC, YC, XfL and TL. DC and TL were serving as guarantor and corresponding author of this study. All authors approved the final manuscript and agreed to submit the protocol in the journal.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and stated that there is no organization to support the submission; no organization is interested in the submitted work; no other relationships or activities effect the submitted work.

Provenance and peer review

Not commissioned; externally peer reviewed

Patient consent for publication

Not required.

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A sample Pubmed search strategy was as follows:

#1 Breast Neoplasm [MeSH Terms]

#2 breast neoplasm [title/abstract]

#3 neoplasm, breast [title/abstract]

#4 breast tumors [title/abstract]

#5 breast tumor [title/abstract]

#6 tumor, breast [title/abstract]

#7 tumors, breast [title/abstract]

#8 neoplasms, breast [title/abstract]

#9 breast cancer [title/abstract]

#10 cancer, breast [title/abstract]

#11 mammary cancer [title/abstract]

#12 cancer, mammary [title/abstract]

#13 cancers, mammary [title/abstract]

#14 mammary cancers [title/abstract]

#15 malignant neoplasm of breast [title/abstract]

#16 breast malignant neoplasm [title/abstract]

#17 breast malignant neoplasms [title/abstract]

#18 malignant tumor of breast [title/abstract]

#19 breast malignant tumor [title/abstract]

#20 cancer of breast [title/abstract]

#21 cancer of the breast [title/abstract]

#22 mammary carcinoma, human [title/abstract]

#23 carcinoma, human mammary [title/abstract]

#24 carcinomas, human mammary [title/abstract]

#25 human mammary carcinomas [title/abstract]

#26 mammary carcinomas, human [title/abstract]

#27 human mammary carcinoma [title/abstract]

#28 mammary neoplasms, human [title/abstract]

#29 human mammary neoplasms [title/abstract]

#30 human mammary neoplasms [title/abstract]

#31 neoplasm, human mammary [title/abstract]

#32 neoplasms, human mammary [title/abstract]

#33 mammary neoplasm, human [title/abstract]

#34 breast carcinoma [title/abstract]

#35 breast carcinomas [title/abstract]

#36 carcinoma, breast [title/abstract]

#37 carcinomas, breast [title/abstract]

#38 breast malignant tumors [title/abstract]

#39 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38

#40 Genes, erbB-2[MeSH Terms]

#41 c-erbB-2 Genes[Title/Abstract]

#42 c erbB 2 Genes[Title/Abstract]

#43 c-erbB-2 Gene[Title/Abstract]

#44 Genes, erbb2[Title/Abstract]

#45 Gene, erbb2[Title/Abstract]

#46 erbb2 Gene[Title/Abstract]

#47 erbb2 Genes[Title/Abstract]

#48 Genes, HER-2[Title/Abstract]

#49 HER-2 Gene[Title/Abstract]

#50 HER-2 Genes[Title/Abstract]

#51 Genes, neu[Title/Abstract]

#52 neu Gene[Title/Abstract]

#53 neu Genes[Title/Abstract]

#54 Genes, HER2[Title/Abstract]

#55 Gene, HER2[Title/Abstract]

#56 HER2 Gene[Title/Abstract]

#57 HER2 Genes[Title/Abstract]

#58 erbB-2 Genes[Title/Abstract]

#59 erbB 2 Genes[Title/Abstract]

#60 erbB-2 Gene[Title/Abstract]

#61 c-erbB-2 Proto-Oncogenes[Title/Abstract]

#62 c erbB 2 Proto Oncogenes[Title/Abstract]

#63 c-erbB-2 Proto-Oncogene[Title/Abstract]

#64 #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63

#65 Trastuzumab[MeSH Terms]

#66 Herceptin[Title/Abstract]

#67 #65 OR #66

#68 #39 AND #64 AND #67

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	16
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-8, supplementary

			file
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11-12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Optimum duration of adjuvant trastuzumab in treatment of human epidermal growth factor receptor-2 positive early breast cancer: protocol for a network meta-analysis of randomized controlled trials

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Optimum duration of adjuvant trastuzumab in treatment of human epidermal growth factor receptor-2 positive early breast cancer: protocol for a network meta-analysis of randomized controlled trials

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Abstract

Introduction: Controversy regarding optimum duration of trastuzumab treatment remains in patients with human epidermal growth factor receptor-2 (HER2) positive early breast cancer. The objective of applying network meta-analysis (NMA) is to integrate existing evidence based on direct and indirect comparisons of efficacy and safety, and then to determine the duration of trastuzumab treatments with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.

Methods and analysis: Electronic searching of trastuzumab treatments for early breast cancer by titles and abstracts will be conducted for the period from inception to June 16, 2019 in PubMed, Cochrane Library, Embase and ClinicalTrils.gov, as well as the annual meetings of San Antonio Breast Cancer Symposium (SABCS), European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) online archives. The outcomes of interest are overall survival, disease-free survival, acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities. Two independent reviewers will screen and extract eligible data based on the inclusion and exclusion criteria, and then assess the risk of bias and evidence quality of individual studies using Cochrane Collaboration's tool and Grades of Recommendation, Assessment, Development and Evaluation (GRADE). The heterogeneity, transitivity and inconsistency of NMA will be evaluated. In addition, we

will perform subgroup and sensitivity analyses to assess the robustness and reliability of findings in our NMA.

Ethics and dissemination: Ethics approval is not required for our NMA. Findings from our NMA will be submitted as peer-reviewed journal manuscripts and international conference reports.

Strengths and limitations of this study

- Our objective of applying NMA is to integrate existing evidence based on direct and indirect comparisons of efficacy and safety, and to determine the duration of trastuzumab treatments with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.
- Our study findings will help clinicians, patients and policy makers to reduce the uncertainty of escalating and de-escalating duration treatment and to select the optimum duration of trastuzumab treatment with highest efficacy and safety.
- We will perform subgroup and sensitivity analyses to assess the robustness and reliability of NMA results.
- Language bias is the potential limitation of our study as NMA will only include published studies in English.

Trial registration number CRD42019139109

Keywords: early breast cancer, human epidermal growth factor receptor-2, trastuzumab, network meta-analysis, protocol

Introduction

Human epidermal growth factor receptor-2 (HER2) positive breast cancer accounts for approximately 20–25% of overall reported cases(1,2) and is associated with poor prognosis.(3,4) Trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 protein, is used for patients with HER2-positive early breast cancer. (5-7) Recently, targeted therapy using one year of trastuzumab has been proven to improve overall survival (OS) and disease-free survival (DFS) significantly in early HER2-positive breast cancer. (8-11) Compared to treatment using chemotherapy only in early HER2-positive breast cancer, treatment using adjuvant trastuzumab plus chemotherapy tends to reduce the risk of recurrence and death by one-third. (12)

However, the optimal duration of trastuzumab treatment has been an intense controversy and ongoing debate in terms of efficacy, toxicity, convenience and cost.(13) High-quality randomized controlled trials (RCTs) have confirmed that multiple treatment durations of trastuzumab were effective for HER2-positive early breast cancers, but the relative efficacy and safety were not evaluated for all head-to-head trials. More specifically, the HERceptin Adjuvant (HERA) trial has confirmed that 24 months of adjuvant trastuzumab treatment, which was associated with a higher cost, inconvenience and cardiac toxicity (7.3% vs 4.4%), would

not improve DFS compared to a 12 months of adjuvant therapy treatment [hazard ratio (HR) 1.02, 95% confidence intervals (CI) 0.89–1.17]. (14) While comparing to the 12 months of trastuzumab treatment, six months of trastuzumab treatment was non-inferior and associated with decreased cardiac toxicity (8% vs 4%, $P<0.001$) in the PERSEPHONE trial, but was not non-inferior in the PHARE and HORG trials.(15-17) In contrast, the SOLD and Short-HER trials applying nine weeks of trastuzumab was not non-inferior compared to the 12 months of trastuzumab, and a significant reduction in cardiac toxicity was observed in nine weeks of trastuzumab. (18,19)

Direct comparison among preventive strategies was limited, as half of RCTs, including N9831, NSABP-B31, BCIRG 006 and FinHER trials, comparing active therapy to inactive interventions (e.g., placebo). (10,11,20) Pivotal pairwise meta-analyses have been used to evaluate the efficacy and toxicity between shorter durations of trastuzumab and standard option directly. The analyses results suggested that 12 months of trastuzumab would still be the optimal treatment for early HER2-positive breast cancer, albeit with a significant increase in cardiac events. (13,21-24) The latest pairwise meta-analysis indicated that the use of trastuzumab in a one-week cycle with anthracycline-taxane chemotherapy regimens simultaneously seemed to be the preferred option to optimize its efficacy and safety regardless of the duration of

trastuzumab administration. (12) However, the results were only from subgroup analysis, and the courses of trastuzumab administration were not only 12 months but also nine weeks. Without direct comparison of RCTs, they did not contain 12 weeks, six months and 24 months of trastuzumab concurrently with chemotherapy compared with chemotherapy alone for early HER2-positive breast cancer in pairwise meta-analysis.

These intriguing results provoked an intense debate on consideration escalating and de-escalating duration treatment as new standard of care. Network meta-analysis (NMA) will provide indirect evaluations on the relative efficacy and toxicity of multiple durations of adjuvant trastuzumab therapies in HER2-positive early breast cancer. (25) To address the aforementioned debate and determine the most appropriate treatment options, we will conduct NMA to integrate existing evidence available, based on direct and indirect comparisons of efficacy and safety, and to determine the duration of trastuzumab treatments (24 months vs 12 months vs six months vs 12weeks vs nine weeks vs placebo/observation/zero) with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.

Methods

The results of our protocol will be evaluated in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

(PRISMA-P).(26) Similarly, we will perform NMA in guidance of the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions. (27) This project has been registered in PROSPERO (CRD42019139109).

Search strategy

Electronic searching by titles and abstracts of trastuzumab treatments for early breast cancers will be performed in PubMed, Cochrane Library, Embase (Ovid interface) and ClinicalTrials.gov, as well as the annual meetings of San Antonio Breast Cancer Symposium (SABCS) (2015-2019), European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) online archives until June 16, 2019. Two reviewers who have been trained in data extraction will conduct search strategies independently. The same two authors will search reference lists manually from eligible reviews and relevant trials to identify additional potential papers. We will record the reasons of excluding the full text and generate a PRISMA flow diagram for the NMA. (28)

The terms used for literature searching will include the following domains of Medical Subject Heading (MeSH) terms: ‘breast cancer’, ‘human epidermal growth factor receptor-2’ and ‘trastuzumab’, according to Population Intervention Comparison Outcomes Study Design (PICOS) statement. MeSH and Subheadings will be combined with ‘AND’ or

'OR'. The complete search strategy is presented in online supplementary file 1 (see the appendix 1).

We will perform a pilot test to evaluate inter-rater reliability and adjust each screening stage: title and abstract, followed by full-text screening. Two independent reviewers will screen the titles and abstracts of related studies based on inclusion and exclusion criteria. The eligible or potentially eligible trials will be evaluated by reading through the full texts when necessary. Moreover, disagreements in data extraction will be discussed with the help of the third reviewer.

Eligibility criteria

Trials will be eligible if they fulfill the following criteria: 1. Populations: patients with HER2-positive early breast cancer of any age or nationality were treated with trastuzumab treatments; 2. Interventions: any duration of trastuzumab treatments were given. We are also interested in the impact of placebo/observation/zero as adjuvant treatment; 3. Comparators: 12 months of trastuzumab treatment was compared with placebo/observation/zero, or other durations of adjuvant trastuzumab; 4. Outcomes: OS, DFS, acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities; 5. Study design: RCTs that compared any two or more different arms of adjuvant trastuzumab in patients with HER2-positive early breast cancer; 6. Language and other limitations: We will include studies published in English regardless of publication status.

Studies not meeting the inclusion criteria will be excluded. The other excluding criteria are as follows: 1. Neoadjuvant and adjuvant treatment with trastuzumab biosimilars; 2. Palliative care with trastuzumab.

Outcomes

The outcomes of interest are OS (defined as the time from randomization to death from any cause), DFS (defined as the time from randomization to local, regional, distant relapse, contralateral breast cancer, second primary cancer, or death from any cause, whichever occurred first), acceptability (defined as the proportion of patients who discontinued trastuzumab), cardiotoxicities, and grade 3-4 nonhematologic toxicities. The cardiac toxicity grading is used by the Common Terminology Criteria for Adverse Events of the National Cancer Institute. Cardiac toxicity is defined as an asymptomatic decline in left ventricular ejection fraction (LVEF) to ≤45%, an absolute drop of 10-15% in follow-up echocardiography, symptomatic congestive heart failure (New York Heart Association [NYHA] class III/IV) or cardiac death.(29,30) We will calculate the relative effectiveness for each network comparison among all duration of treatments with trastuzumab. (31)

Data extraction and management

The management of literature searching records will be carried out in EndNote X7. A spreadsheet will be created in Microsoft Excel 2010

(Microsoft Corp, Redmond, WA, www.microsoft.com) to collect outcomes of interest, such as study ID, first author, study design, recruitment time frame, detailed interventions, sample size, and endpoints (OS, DFS, acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities). We will contact corresponding authors and relevant pharmaceutical companies for further information if important data are not reported in articles. The most up-to-date data will be included if duplicate publications are identified.

Bias risk

The risk of bias of RCTs in the NMA will be evaluated by reviewer manager according to the following domains outlined in the Cochrane Collaboration's tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.(32) Two authors will review RCTs independently and report a high risk of bias as "-", a low risk of bias as "+", or an unclear risk of bias as "?". Any disagreements in assessment of risk of bias will be resolved by discussion, or the help of the third reviewer if needed.

Quality of evidence

We will evaluate the quality of evidence of individual studies using Grades of Recommendation, Assessment, Development and Evaluation

(GRADE), which is based on the following five domains: risk of bias, imprecision, inconsistency, indirectness and publication bias.(33,34) The staging system categories for GRADE evidences are scored as high, moderate, low or very low quality. The initial confidence level for each RCT is set as high, but will be rated down based on the evaluation of the five domains. The strength of evidences will also be graded for the outcomes based on GRADE system in CINeMA. (34)

Statistical analysis

We will perform the traditional pairwise meta-analysis on direct comparisons based on two or more studies with Stata13.0 (StataCorp, College Station, TX, USA). To compare eligible interventions directly and indirectly, NMA displaying outcomes of interest is planned using WinBUGS version1.4.3 (MRC Biostatistics Unit, Cambridge, UK). Pooled hazard ratios (HRs) for OS and DFS with 95% confidence intervals (CIs) will be calculated using both fixed- and random-effects models. Binary outcomes (acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities) are expressed as odds ratios (ORs) with 95% CI. The results of comparative effectiveness and safety probability statements of intervention effects will be ranked; and rank plots across all outcomes will be generated. The interventions with surface under the cumulative ranking (SUCRA) in term of efficacy and safety will be evaluated to interpret relative effect of comparisons. We

will compare the risk-benefit profile of all comparators in terms of efficacy and toxicity. A two-sided $p< 0.05$ is considered statistically significant.

We will estimate the presence of heterogeneity based on the magnitude of I^2 estimated from pairwise meta-analysis models. The heterogeneity is considered as evidence of low if I^2 <25%, as moderate if 25% ≤ I^2 ≤ 50%, and as high if I^2 >50%. (35) The fixed-effects models will be used when the heterogeneity is low and moderate; otherwise, a random-effects models will be used. In addition, we will also evaluate the transitivity and inconsistency of NMA. The transitivity will be assessed by applying descriptive statistics for study types and demographic characteristics. Inconsistency will be assessed by comparing deviation information criteria (DIC) statistics in the fitted consistency and inconsistency models. (36) Global inconsistency between direct and indirect comparisons will also be evaluated by using a loop-specific method, if a loop connecting three or more arms exists. (37)

Subgroup analysis

We will explore whether specific duration of treatments with trastuzumab might be more appropriate for particular subtypes of breast cancer. We categorize breast cancer into the following groups when possible: Estrogen Receptor (ER) positive, ER negative, node positive and node negative.

Sensitivity analysis

We will perform sensitivity analyses to assess the robustness and reliability of findings in our NMA. In order to check the impact of HER2 status on the results, the first sensitivity analysis will exclude patients with HER2 negative after re-evaluating the HER2 status in the E2198 trial. (38) The second sensitivity analysis will restrict hormone receptor-positive to ER + and PR +, ER + and PR -, ER - and PR +. Lastly, the sensitivity analysis will classify patients as 1-3 and ≥4 positive lymph nodes to specify the impact of the number of positive lymph nodes.

Discussion

Despite trastuzumab being highly effective in treatment for HER2-positive early breast cancer, its substantial socio-economic burden attracted the attention of governments, academic researchers, pharmaceutical companies and health care payers. With the consideration of balancing efficacy and cardiotoxicity, the 12-month and six-month of trastuzumab treatments have received increasing interests. The requirement to balance efficacy and side effects (i.e. cardiotoxicity) has led to raise interest in reducing trastuzumab duration from 12 months to six months. With the increase in rates of patients reporting 12-month trastuzumab induced cardiotoxicity, most clinicians suggested that a drop to 83% four-year DFS with six months trastuzumab would be also

acceptable. (39) This benefit-risk analysis will provide important information to help clinicians, patients and policy makers to decide optimum duration of adjuvant treatment with trastuzumab in their daily practice.

The 12 months of treatments with trastuzumab for most women with early HER2 positive breast cancer was a standard of care, but most crucial RCTs mainly focused on patients with high-risk of recurrence and one-year duration was chosen arbitrarily. In contrary, a particular subtype of patients might be appropriate for de-escalating duration of treatment, without compromising efficacy. Romualdo and his colleagues deemed that de-escalating chemotherapy was a good option for older patients and those with stage I HER2-positive breast cancer. (40) This study will explore whether de-escalating targeted therapy is another option for patients with particular subtypes (ER positive and node negative).

As far as we know, the results of system review will fill a pivotal knowledge gap of optimal duration of adjuvant trastuzumab in patients with early HER2 positive breast cancer. We hope the findings from this NMA will help clinicians, patients and policy makers to select optimal duration of adjuvant trastuzumab with the greatest value in HER2 positive early breast cancers. It will also provide a result that will engage patients and policy makers, and will contribute to the public debate on future policy options. Furthermore, under-recognized comparisons (e.g.,

six months vs nine weeks) may be identified by this Bayesian analysis to guide future research.

Patient and public involvement

The manuscript was developed without patient or public participation. Breast cancer patient organizations will participate in the discussion and dissemination of research results. A summary of the findings will be provided to the Chinese society of clinical oncology (CSCO).

Ethics and dissemination

An ethics approval is not required for the NMA. Important modifications to the study protocol will be communicated to all members of the research team. The results will be disseminated through international conference reports and published in a peer-reviewed journal.

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Author contributions

QcH and DC conceptualized the network meta-analysis. QcH and XW co-developed the search strategy. Both QcH and XW were major contributors in writing the manuscript. The protocol was revised by DC, YC, XfL and TL. DC and TL were serving as guarantor and corresponding author of this study. All authors approved the final manuscript and agreed to submit the protocol in the journal.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and stated that there is no organization to support the submission; no organization is interested in the submitted work; no other relationships or activities effect the submitted work.

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Patient consent for publication

Not required.

References:

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A sample Pubmed search strategy was as follows:

#1 Breast Neoplasm [MeSH Terms]

#2 breast neoplasm [title/abstract]

#3 neoplasm, breast [title/abstract]

#4 breast tumors [title/abstract]

#5 breast tumor [title/abstract]

#6 tumor, breast [title/abstract]

#7 tumors, breast [title/abstract]

#8 neoplasms, breast [title/abstract]

#9 breast cancer [title/abstract]

#10 cancer, breast [title/abstract]

#11 mammary cancer [title/abstract]

#12 cancer, mammary [title/abstract]

#13 cancers, mammary [title/abstract]

#14 mammary cancers [title/abstract]

#15 malignant neoplasm of breast [title/abstract]

#16 breast malignant neoplasm [title/abstract]

#17 breast malignant neoplasms [title/abstract]

#18 malignant tumor of breast [title/abstract]

#19 breast malignant tumor [title/abstract]

#20 cancer of breast [title/abstract]

#21 cancer of the breast [title/abstract]

#22 mammary carcinoma, human [title/abstract]

#23 carcinoma, human mammary [title/abstract]

#24 carcinomas, human mammary [title/abstract]

#25 human mammary carcinomas [title/abstract]

#26 mammary carcinomas, human [title/abstract]

#27 human mammary carcinoma [title/abstract]

#28 mammary neoplasms, human [title/abstract]

#29 human mammary neoplasms [title/abstract]

#30 human mammary neoplasms [title/abstract]

#31 neoplasm, human mammary [title/abstract]

#32 neoplasms, human mammary [title/abstract]

#33 mammary neoplasm, human [title/abstract]

#34 breast carcinoma [title/abstract]

#35 breast carcinomas [title/abstract]

#36 carcinoma, breast [title/abstract]

#37 carcinomas, breast [title/abstract]

#38 breast malignant tumors [title/abstract]

#39 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38

#40 Genes, erbB-2[MeSH Terms]

#41 c-erbB-2 Genes[Title/Abstract]

#42 c erbB 2 Genes[Title/Abstract]

#43 c-erbB-2 Gene[Title/Abstract]

#44 Genes, erbb2[Title/Abstract]

#45 Gene, erbb2[Title/Abstract]

#46 erbb2 Gene[Title/Abstract]

#47 erbb2 Genes[Title/Abstract]

#48 Genes, HER-2[Title/Abstract]

#49 HER-2 Gene[Title/Abstract]

#50 HER-2 Genes[Title/Abstract]

#51 Genes, neu[Title/Abstract]

#52 neu Gene[Title/Abstract]

#53 neu Genes[Title/Abstract]

#54 Genes, HER2[Title/Abstract]

#55 Gene, HER2[Title/Abstract]

#56 HER2 Gene[Title/Abstract]

#57 HER2 Genes[Title/Abstract]

#58 erbB-2 Genes[Title/Abstract]

#59 erbB 2 Genes[Title/Abstract]

#60 erbB-2 Gene[Title/Abstract]

#61 c-erbB-2 Proto-Oncogenes[Title/Abstract]

#62 c erbB 2 Proto Oncogenes[Title/Abstract]

#63 c-erbB-2 Proto-Oncogene[Title/Abstract]

#64 #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63

#65 Trastuzumab[MeSH Terms]

#66 Herceptin[Title/Abstract]

#67 #65 OR #66

#68 #39 AND #64 AND #67

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	16
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-8, supplementary

			file
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11-12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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