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Efficacy and safety of neoadjuvant therapy for HR-positive/HER2-negative early breast cancer: a Bayesian network meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 April 2024 and was last updated on 22 April 2024.

INTRODUCTION

Review question / Objective Neoadjuvant treatment for hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer is controversial and requires a comprehensive analysis for optimal therapy assessment. Therefore, a two-step Bayesian network meta-analysis (NMA) was performed to compare the efficacy and safety of different neoadjuvant regimens.

Condition being studied Breast cancer (BC) is the most common cancer among women globally, and the HR+/HER2- subtype constitutes a significant proportion of cases. Neoadjuvant therapy is increasingly incorporated into BC treatment to render inoperable tumors operable and enhance prognosis. However, the efficacy of neoadjuvant therapy in HR+/HER2- BC is still debated. With the introduction of new agents, including CDK4/6 inhibitors, PARP inhibitors, and PD-1/PD-L1 inhibitors, there is potential to improve treatment outcomes in this patient group. We believe that our study makes a significant contribution because it addresses several gaps in the existing literature. Previous network meta-analysis focused mainly on endocrine therapy regimens and did not include chemotherapy, targeted therapy, or immunotherapy. Furthermore, they primarily assessed ORR and safety without including PCR in their outcomes.

METHODS

Participant or population HR+/HER2- early breast cancer patients receiving neoadjuvant therapy.

Intervention Different neoadjuvant treatments.

Comparator Different neoadjuvant treatments.

Study designs to be included Phase II or III randomized clinical trials for neoadjuvant therapy in HR+/HER2- BC, comparing multiple treatments and assessing outcomes such as ORR, PCR, grade 3–5 side effects, and dropout rates.

Eligibility criteria (i) Phase II or III randomized clinical trials (RCTs) that focused on neoadjuvant therapy for HR+/HER2- BC; (ii) trials comparing two or more treatment arms; and (iii) availability of relevant outcome measures, such as ORR, PCR, grade 3–5 side effects data, and dropout events.

Information sources We conducted a comprehensive systematic search of databases, such as PubMed, Embase, and the Cochrane Central Register of Clinical Trials. Additionally, we extensively searched for online articles from the American Society of Clinical Oncology, European Society for Medical Oncology, and San Antonio Breast Cancer Symposium. Our search strategy utilized predefined keywords: (neoadjuvant OR preoperative) AND (treatment OR therapy OR chemotherapy OR endocrine therapy OR target therapy) AND (breast OR mammary) AND (cancer OR carcinoma OR malignant OR neoplasm OR tumor) AND (hormone receptor-positive OR HR-positive OR HR+ OR estrogen receptor-positive OR ER+ OR ER-positive OR progesterone receptor-positive OR PR-positive OR PR+ OR Luminal) AND (HER-2- OR HER2- OR ERBB2- OR HER-2 negative OR HER2 negative OR ERBB2 negative OR human epidermal growth factor receptor 2 negative).

Main outcome(s) (1) Objective response rate (ORR) was defined as the sum of partial and complete responses according to the Modified Response Evaluation Criteria in Solid Tumors (version 1.1) by MRI, US, or physical examination. (2) Pathologic complete response (PCR) was defined as the absence of invasive residual cancer in the breast tissue and lymph nodes (ypT0/is ypN0) according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edition. (3)Dropout events were defined as the cause of patient withdrawal from the trial due to adverse events.

Quality assessment / Risk of bias analysis We assessed the risk of bias in the included RCTs using the Cochrane Risk of Bias (ROB) 2.0 tool [19], which was used to examine the following five dimensions: (1) randomization process, (2) bias of the intended intervention, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of reported outcomes. Disagreements between authors were resolved through discussion. Publication bias was evaluated by analyzing the symmetry of the funnel plot features, which was generated using STATA. The symmetrical and focused arrangement of points within the funnel plots suggested the absence of significant bias. Asymmetry in the funnel plots prompted further evaluation using Egger's test.

Strategy of data synthesis In the analysis of direct and indirect comparisons, effect sizes were pooled using odds ratios (OR) and 95% confidence intervals (95% CI) because the outcomes were dichotomous variables. Direct evidence was integrated through a pairwise meta-analysis using Review Manager software (version 5.4). Heterogeneity was assessed using the Mantel-Haenszel chi-square test and I^2 test. We defined an I^2 above 50% as indicating a large between-study heterogeneity. The results of the direct comparison were calculated using either a fixed or random-effects model based on the value of I^2. For the Bayesian network meta-analysis, Markov chain Monte Carlo (MCMC) methods were employed using Stata (version 14) and R (version 4.2.3). Three Markov chains were run simultaneously for 50,000 iterations, with different initial values. Given the heterogeneity observed across the different clinical trials, a random-effects model was used to estimate each outcome. The ranking of the different treatments was determined using the network rank and surface under the cumulative ranking (SUCRA), where higher SUCRA values indicated higher ORR/PCR rates.

Subgroup analysis Perform subgroup analysis based on menopausal status.

Sensitivity analysis Leave-one-out analysis: This method involves sequentially excluding each study or each treatment comparison, and then re-analyzing the meta-analysis to assess the influence of each study on the overall result. This helps determine whether certain studies or treatment comparisons have a significant impact on the synthesized effect.
Model sensitivity analysis: The statistical models used in network meta-analysis may have different assumptions and parameter choices. By changing the assumptions or parameters of the model and re-analyzing the meta-analysis, the impact of these assumptions and parameter choices on the results can be evaluated.
Subgroup analysis: In network meta-analysis, studies can be divided into different subgroups

based on various characteristics (such as study quality, study design, characteristics of study participants, etc.), and then meta-analyzed separately. This helps to examine whether there are differences between different subgroups.

Language restriction English.

Country(ies) involved China.

Keywords breast cancer, chemotherapy, endocrine therapy, hormone receptor-positive/human epidermal growth factor receptor 2-negative, immunotherapy, neoadjuvant, network meta-analysis.

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