INPLASY PROTOCOL

To cite: Zhang et al. Adjuvant and neoadjuvant therapy of cyclin-dependent kinase 4 and 6 inhibitors in hormone receptor-positive, human epidermal growth factor receptor 2-negative, early breast cancer: a systematic review and meta-analysis. Inplasy protocol 2022110008. doi: 10.37766/inplasy2022.11.0008

Received: 02 November 2022

Published: 02 November 2022

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Support: **NSFC.**

Review Stage at time of this submission: **Completed but not published.**

Conflicts of interest:
None declared.

Adjuvant and neoadjuvant therapy of cyclin-dependent kinase 4 and 6 inhibitors in hormone receptor-positive, human epidermal growth factor receptor 2-negative, early breast cancer: a systematic review and meta-analysis

Zhang, ML[1]; Song, J[2]; Yang, HG[3]; Jin, F[4]; Zheng, A[5].

Review question / Objective: **The purpose of this study was to evaluate the efficacy and safety of CDK4/6 inhibitor combined with endocrine therapy (ET) in patients with HR+, HER2- early breast cancer.**
Eligibility criteria: **We included (i) studies conducted among patients who were pathologically diagnosed with HR+ HER2- early breast cancer; (ii) phase II/III studies; (iii) studies that comprised an experimental group (which consisted of those who received CDK4/6 inhibitors in combination with ET) and a control group (which consisted of patients who received ET with or without placebo); (iv) studies whose endpoints were invasive disease-free survival (IDFS), distant relapse-free survival (DRFS), complete cell-cycle arrest (CCCA), or AEs; and (v) studies that directly extracted or calculated the hazard ratios, odds ratio (OR), risk ratio (RR), and 95% confidence interval (CI).Meanwhile, (i) phase I and single-arm tests; (ii) non-RCTs; (iii) systematic review, case reports, comments, and animal studies; (iv) studies whose available data and relevant outcomes were not extracted; and (v) incomplete or ongoing studies were excluded.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 November 2022 and was last updated on 02 November 2022 (registration number INPLASY2022110008).

INTRODUCTION

Review question / Objective: **The purpose of this study was to evaluate the efficacy and safety of CDK4/6 inhibitor combined with endocrine therapy (ET) in patients with HR+, HER2- early breast cancer.**

Condition being studied: **In patients with advanced breast cancer with HR+ HER2-, multiple clinical studies have demonstrated**

that CDK4/6 inhibitors combined with aromatase inhibitors or fulvestrant groups can significantly delay disease progression and reduce the risk of death, and that most adverse events (AEs) are controllable. Obviously, the application of CDK4/6 inhibitors has improved the clinical treatment mode of patients with advanced breast cancer, so it raises our interest whether we can benefit in patients with early breast cancer with HR+ HER2-. The goal of treatment for advanced and early breast cancer is different, with advanced breast cancer aimed at prolonging survival and early breast cancer usually aimed at cure. The tumor burden, tumor microenvironment and host body state were different in the two stages. Therefore, the application of drugs that demonstrate therapeutic value in advanced breast cancer in early-stage patients needs to be further explored. The reported efficacy of CDK4/6 inhibitors combination and ET in HR+ HER2- early breast cancer is controversial, with varying results across major clinical trials. Therefore, this meta-analysis included all available randomized controlled trials (RCTs) with the aim to explore the efficacy and safety of CDK4/6 inhibitors plus ET in patients with HR+ HER2- early breast cancer receiving adjuvant or neoadjuvant therapy. Accurate prediction of breast cancer populations that can benefit from CDK4/6 inhibitors therapy, and provide new evidence for clinical diagnosis and treatment.

METHODS

Participant or population: Patients who were pathologically diagnosed with HR+ HER2- early breast cancerpatients with breast cancer.

Intervention: Patients received CDK4/6 inhibitors in combination with ET.

Comparator: Patients who received ET with or without placebo.

Study designs to be included: We included (i) studies conducted among patients who were pathologically diagnosed with HR+ HER2- early breast cancer; (ii) phase II/III studies; (iii) studies that comprised an experimental group (which consisted of those who received CDK4/6 inhibitors in combination with ET) and a control group (which consisted of patients who received ET with or without placebo); (iv) studies whose endpoints were invasive disease-free survival (IDFS), distant relapse-free survival (DRFS), complete cell-cycle arrest (CCCA), or AEs; and (v) studies that directly extracted or calculated the hazard ratios, odds

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Information sources: PubMed, Embase, Cochrane Library, and Web of Science.

Main outcome(s): Eight articles (including six RCTs) were included in the study. In adjuvant therapy, CDK4/6 inhibitors combined with ET improved IDFS [hazard ratio = 0.85, 95% confidence interval (CI) 0.69-1.05, P = 0.13] and DRFS (hazard ratio = 0.85, 95%CI 0.56-1.28, P = 0.44) in early breast cancer patients versus ET with or without placebo, but the difference was not statistically significant. In neoadjuvant therapy, CDK4/6 inhibitors combined with ET significantly improved CCCA compared with control group (odds ratio = 9.00,

95%CI 5.42-14.96, P < 0.00001). In terms of safety, the combination treatment group significantly increased the incidence of grade 3-4 hematological AEs in patients, especially grade 3-4 neutropenia [risk ratio (RR) = 64.74, 95%CI 16.26-257.86, P < 0.00001] and grade 3-4 leukopenia (RR = 85.81, 95%CI 19.05-386.45, P < 0.00001) with statistically significant differences.

Quality assessment / Risk of bias analysis: The quality of RCTs was evaluated using the Cochrane Collaboration tool (10). The process was completed using the Review Manager, version 5.3. The criteria used to assess the quality of the literature were as follows: (i) random sequence, (ii) allocation concealment, (iii) blinding of participants and personnel, (iv) blinding of outcomes, (v) incomplete outcome data, (vi) selective reporting, and (vii) other biases: "low-risk," "high-risk," and "unclear." Two researchers (Meilin Zhang and Ang Zheng) independently assessed the quality of the literature and resolved the differences through discussion until a consensus was reached.

Strategy of data synthesis: This study was carried out using the Review Manager software (version 5.3). The IDFS and DRFS were analyzed using HR and 95% CI, and subgroup analyses were performed based on the baseline characteristics of the patients. The CCCA and AEs were analyzed using OR and RRs. The statistical significance was set at P < 0.05. Heterogeneity was judged according to the results of Cochran's Q and I^2 tests. A Cochran Q statistic of P < 0.1 or an I^2 of >50% indicated heterogeneity among the included studies, using the random-effects model and sensitivity analysis, if necessary. The fixed-effects model was used when the Cochran Q statistic was P > 0.1 and I^2 was <50%.

Subgroup analysis: The IDFS and DRFS were analyzed using HR and 95% CI, and subgroup analyses were performed based on the baseline characteristics of the patients.

Sensitivity analysis: A Cochran Q statistic of P < 0.1 or an I^2 of >50% indicated heterogeneity among the included studies, using the random-effects model and sensitivity analysis, if necessary.

Country(ies) involved: China.

Keywords: early breast cancer; CDK4/6 inhibitors; endocrine therapy; randomized controlled trial.

Contributions of each author:
Author 1 - Meilin Zhang.
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