INPLASY

Identifying Subgroups Deriving the Most Benefit from PD-1 Checkpoint Inhibition plus Chemotherapy in Advanced Metastatic Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - None.

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

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 24 April 2024 and was last updated on 24 April 2024.

INTRODUCTION

Review question / Objective What is the extent of progression-free survival (PFS) enhancement observed in various subgroups of metastatic triple-negative breast cancer (TNBC) patients when treated with a combination of immunotherapy and chemotherapy, compared to chemotherapy alone?

Rationale This study aims to address the pressing need for improved treatment strategies for metastatic triple-negative breast cancer (mTNBC), a subtype associated with aggressive characteristics and limited targeted treatment options. Despite exhibiting heightened response to chemotherapy, mTNBC patients often face high rates of recurrence and poor survival, necessitating alternative therapeutic approaches. Immunotherapy, particularly PD-1/PD-L1 inhibitors, has emerged as a promising avenue due to TNBC's high expression of PD-L1 and infiltration of tumor-infiltrating lymphocytes (TILs).

Combining immunotherapy with chemotherapy has shown improved outcomes in various cancers, including breast cancer, leading to recent approvals for this approach in mTNBC. However, the extent of benefit across different patient subgroups remains unclear. Factors such as PD-L1 expression, age, race, and prior chemotherapy exposure may influence immunotherapy response.

Through a comprehensive systematic review and meta-analysis, this study seeks to elucidate how these patient- and treatment-related factors impact the effectiveness of immunotherapy in mTNBC. By conducting subgroup analyses, we aim to identify specific patient cohorts that derive significant progression-free survival (PFS) benefits from the combination of immunotherapy and chemotherapy. Ultimately, this research has the potential to inform

personalized treatment strategies and improve outcomes for individuals with mTNBC.

Condition being studied Triple-negative breast cancer (TNBC) represents 15–20% of breast cancer cases and poses a significant clinical challenge due to its aggressive nature and lack of specific targeted therapies. Characterized by highly proliferative, high-grade, and basal-like genetic features (present in approximately 55–81% of cases), TNBC typically lacks expression of hormone receptors (estrogen receptor [ER] and progesterone receptor [PR]) and does not exhibit amplification or overexpression of human epidermal growth factor receptor 2 [HER2]. Consequently, treatment options for TNBC are limited, necessitating reliance primarily on cytotoxic chemotherapy as the cornerstone of therapy.

METHODS

Search strategy PubMed was formally searched for several key terms until Dec 2023. Further potential studies were identified by screening the references of relevant articles. A stepwise procedure comprising retrieval, organization, and screening was followed by two reviewers (S.L. and B.F.) to select studies that met the eligibility criteria. Disagreements were resolved by consulting the corresponding author (M.K.).

Participant or population Advanced metastatic triple-negative breast cancer (TNBC).

Intervention Chemotherapy plus PD-1 checkpoint inhibition immunotherapy.

Comparator Chemotherapy alone.

Study designs to be included Randomized controlled trials (RCTs).

Eligibility criteria Studies were evaluated for eligibility according to the following criteria: 1) Patients with advanced metastatic triple-negative breast cancer (TNBC) receiving chemotherapy with immune checkpoint inhibitors (ICIs); 2) Studies reported the comparison of subgroup for the primary outcome of interest (PFS); 3) Efficacy outcome (PFS) was reported in the form of hazard ratios and corresponding 95% confidence intervals; 4) Only randomized controlled trials (RCTs) were conducted with English-language restrictions.

Information sources PubMed.

Main outcome(s) The primary outcome of interest was comparison of progression-free survival in subgroups of the intention-to-treat (ITT) population, based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Data management Data extraction was performed using the modified form "The Cochrane Collaboration Data Collection form for RCTs" obtained from the Cochrane website. The extracted data included the general characteristics of the included studies, participants, and the main outcomes. The general characteristics of the included studies included the first author, publication year, trial designation, national clinical trial (NCT) registration number, trial design, number and type of participants, treatment protocols, and median duration of follow-up. Participant information included age, race, menopausal status, ECOG (Eastern Cooperative Oncology Group) performance status, PD-L1 expression status, and use of previous chemotherapy. Furthermore, the outcomes of interest (progression-free survival, objective response rates, overall survival, and safety outcomes) for treatment differences were extracted from the papers.

Quality assessment / Risk of bias analysis The Cochrane Collaboration Tool was used to assess the quality of the trials. Assessments included sequence generation, allocation of sequence concealment, blinding of participants and personnel, blinding of outcomes and assessments, incomplete outcome data, selective outcome reporting, and other bias.

Strategy of data synthesis Hazard ratios (HRs) and their corresponding 95% confidence intervals (CI) were extracted for progression-free survival. Natural logarithm of the HRs [ln(HRs)] were taken and standard errors were calculated for individual outcomes according to the following formula: SE=(LN (Upper 95% CI)-LN (Lower 95% CI))/(2*1.96); where LN stands for natural logarithm. Review Manager (RevMan) version 5.4 was used to pool HRs using the inverse variance statistical method. Heterogeneity was assessed using Chi2 test and I2 value and graded as low (I2 = 25%), moderate (I2 =50%), or high (I2 =75%) according to the I2 values. A fixed-effects analysis model was adopted unless the heterogeneity exceeded 50% (I2 ≥ 50%). In this case, a random-effects analysis model was used. The significance level was set at $p < 0.05$.

Subgroup analysis Baseline patient- and treatment-related characteristics were evaluated for association with efficacy derived from

combination of chemotherapy plus immunohterapy, such as age, race, ECOG status, PD-L1 expression, metastatic information and prior exposure to chemotherapy.

Sensitivity analysis Sensitivity analyses were performed using three steps. First, The Cochrane Collaboration Tool was used to assess the quality of the included RCTs. Secondly, heterogeneity was assessed using Chi2 test and I2 value and graded as low (I2 = 25%), moderate (I2 =50%), or high (I2 =75%) according to the I2 values. A fixed-effects analysis model was adopted unless the heterogeneity exceeded 50% (I2 ≥ 50%). In this case, a random-effects analysis model was used. Thirdly, Publication bias was reported for each outcome. Fourth, each time the sensitivity of the outcome was reported in terms of low number of participants, heterogeneity, and results were reported without such study or participants.

Language restriction English.

Country(ies) involved China and Pakistan.

Keywords Breast cancer; immunotherapy; immune checkpoint inhibitors (ICI); pembrolizumab; atezolizumab; progression-free survival.

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