

INPLASY PROTOCOL

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Corresponding author:
Manyu Li

18010150796@163.com

Author Affiliation:
Department of Oncology,
Beijing Chao-Yang Hospital

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None.

The association between proton pump inhibitors use and clinical outcome of patients receiving immune checkpoint inhibitors therapy: A systematic review and meta-analysis

Li, M¹; An G².

Review question / Objective: What is the association between proton pump inhibitors (PPI) use and the efficacy of immune checkpoint inhibitors (ICI) therapy?

Condition being studied: The gut microbiome can mediate the efficacy of immune checkpoint inhibitors (ICI). Meanwhile, proton pump inhibitors (PPI) can modulate the gut microbiome significantly. However, the impact of PPI use on the clinical outcome of ICI therapy remains unclear.

Information sources: We searched for articles in PubMed, EMBASE, and Cochrane Library from their inception date to June 2020. We also expanded our search by reviewing abstracts and presentations from major conferences, including the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) meeting, in order to make sure that all eligible articles could be screened. Finally, references to the studies included in the final selection were also checked.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 July 2020 and was last updated on 24 July 2020 (registration number INPLASY202070108).

INTRODUCTION

Review question / Objective: What is the association between proton pump inhibitors (PPI) use and the efficacy of immune checkpoint inhibitors (ICI) therapy?

Condition being studied: The gut microbiome can mediate the efficacy of immune checkpoint inhibitors (ICI). Meanwhile, proton pump inhibitors (PPI) can modulate the gut microbiome significantly. However, the impact of PPI

use on the clinical outcome of ICI therapy remains unclear.

METHODS

Search strategy: We searched for articles in PubMed, EMBASE, and Cochrane Library. The keywords utilized were as follows: “neoplasm”, “carcinoma”, “malignant neoplasm”, “avelumab”, “atezolizumab”, “camrelizumab”, “cetrelimab”, “nivolumab”, “pembrolizumab”, “bintrafusp alfa”, “envafolimab”, “cemiplimab”, “sintilimab”, “durvalumab”, “pidilizumab”, “toripalimab”, “ipilimumab”, “tislelizumab”, “proton pump inhibitors”, “omeprazole”, “pantoprazole”, “lansoprazole”, “rabeprazole”, “esomeprazole”, “dexlansoprazole”.

Participant or population: Cancer patients treated with ICI.

Intervention: Proton pump inhibitors.

Comparator: Non proton pump inhibitors exposure.

Study designs to be included: Retrospective cohort studies.

Eligibility criteria: (1) studies focusing on patients with solid malignant tumors receiving ICI therapy; (2) providing information concerning hazard ratios (HRs) for overall survival (OS) and/or progression-free survival (PFS) for patients using PPI compared to those who did not.

Information sources: We searched for articles in PubMed, EMBASE, and Cochrane Library from their inception date to June 2020. We also expanded our search by reviewing abstracts and presentations from major conferences, including the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) meeting, in order to make sure that all eligible articles could be screened. Finally, references to the studies included in the final selection were also checked.

Main outcome(s): Overall survival, Progression-free survival.

Data management: The following information was collated from the selected articles: the first author, publication year, type of cancer, region, sample size, immunotherapy agents, PPI use and HR and 95% confidence intervals (CIs) for OS and/or PFS between PPI users and non-users.

Quality assessment / Risk of bias analysis: Risk of bias was assessed based on Newcastle-Ottawa scale. Two reviewers graded the studies from the following aspects: subject selection, comparability, and the evaluation of the outcome.

Strategy of data synthesis: The pooled HR and 95% CIs of OS and PFS were calculated, with HR>1.0 indicating a worse outcome in the PPI user arm. Random-effects models were adopted using Review Manager (RevMan 5.3; The Cochrane Collaboration, Oxford, United Kingdom). Egger’s tests for detecting publication bias and sensitivity analysis were performed using Stata version 15.1 (Stata Corp, College Station, TX).

Subgroup analysis: Subgroup analyses were conducted to explore whether the influence of PPI use varied between different types of cancer.

Sensibility analysis: Sensibility analysis was utilized to examine whether the results could have been influenced by a single study by removing one study at a time. We use STATA 15.1 software to conduct it.

Language: English.

Country(ies) involved: China.

Keywords: Meta-analysis; Immune checkpoint inhibitors; Proton pump inhibitors; Gastrointestinal microbiome; Survival.

Contributions of each author:

Author 1 - Manyu Li.

Author 2 - Guangyu An.