INPLASY PROTOCOL

To cite: Yan et al. Risk of sepsis in cancer patients treated with immune checkpoint inhibitors: a safety meta-analysis of randomized controlled trials. Inplasy protocol 202240174. doi: 10.37766/inplasy2022.4.0174

Received: 29 April 2022

Published: 29 April 2022

Corresponding author:
Miao Yan

yanmiao@csu.edu.cn

Author Affiliation:
Central South University

Support: **N/A.**

Review Stage at time of this submission: **Formal screening of search results against eligibility criteria.**

Conflicts of interest:
None declared.

Risk of sepsis in cancer patients treated with immune checkpoint inhibitors: a safety meta-analysis of randomized controlled trials

Yan, M[1]; Xia, S[2]; Zhao, Y[3].

Review question / Objective: **The aim of this meta-analysis is to estimate the risk of sepsis in cancer patients treated with immune checkpoint inhibitors in randomized controlled trials (RCTs).**
Condition being studied: **Sepsis-related toxicities in cancer patients received immune checkpoint inhibitors.**
Information sources: **Electronic databases:Medline; Embase; Central; Trial registers: ClinicalTrails.gov. EU Clinical Trials Register. International Clinical Trials Registry Platform. Regarding RCTs for which we had neither available adverse events on ClinicalTrials.gov nor available adverse events in publications, corresponding authors or sponsors of the study were contacted by e-mail to provide the required information.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 April 2022 and was last updated on 29 April 2022 (registration number INPLASY202240174).

INTRODUCTION

Review question / Objective: **The aim of this meta-analysis is to estimate the risk of sepsis in cancer patients treated with immune checkpoint inhibitors in randomized controlled trials (RCTs).**

Rationale: **We have started preliminary literatures seaching work and found that the lethal toxicity, sepsis cases, were reported with immune checkpoint inhibitors in several RCTs. A safety analysis is urgently needed to uncover their association.**

Condition being studied: Sepsis-related toxicities in cancer patients received immune checkpoint inhibitors.

METHODS

Search strategy: We wish to include all RCTs including at least 1 immune checkpoint inhibitors. As sepsis-related events are expected to be rare adverse events, we do not expect that such events will be reported in the title or abstract. Firstly, we will search MEDLINE via PubMed (from inception) using a dedicated search algorithm with keywords (medical subject headings) and free-text words related to immune checkpoint inhibitors. Secondly and wherever possible, we have collected all additional data from these clinical trials. We will search (from inception) clinical trial registries through ClinicalTrials.gov (https://ClinicalTrials.gov/) and Cochrane Central Register of Controlled Trials (https://www.cochranelibrary.com/central). Finally, regarding RCTs for which we had neither available adverse events on ClinicalTrials.gov nor available adverse events in publications, corresponding authors or sponsors of the study were consider to contact by e-mail to provide the required information.Ongoing surveillance will be done up to final analyses to identify newly published studies (MEDLINE) or posted results (ClinicalTrials.gov) that might affect the findings of the review. Language: English.

Participant or population: Inclusion: We will include studies examining cancer treated children, adult, and elderly patients. Exclusion: Patients received organ transplant or surgery before immune checkpoint inhibitors therapy are going to be excluded from this study.

Intervention: Administration of any checkpoint inhibitors.

Comparator: Administration of control (placebo or non-placebo).

Study designs to be included: We will include: all randomized RCTs that reported (or not) sepsis-related toxicities outcomes.We will exclude: case reports or case series, case-control (nested) studies, observational studies (retrospective or prospective), single arm studies and non-randomized trials.

Eligibility criteria: Population: Cancer patients, all age. Intervention: checkpoint inhibitors Comparison:placebo or non-placebo Outcome:sepsis-related toxicities Study: randomised controlled trials Language: English.

Information sources: Electronic databases:Medline; Embase; Central; Trial registers: ClinicalTrails.gov. EU Clinical Trials Register. International Clinical Trials Registry Platform. Regarding RCTs for which we had neither available adverse events on ClinicalTrials.gov nor available adverse events in publications, corresponding authors or sponsors of the study were contacted by e-mail to provide the required information.

Main outcome(s): To estimate the risk of sepsis associated with immune checkpoint inhibitors versus placebo (or non-placebo).

Additional outcome(s): (i) to assess the incidence of reported sepsis cases associated with immune checkpoint inhibitors in all RCTs (placebo or non-placebo). (ii) to perform sensitivity and sub-group analyses for exploring possible sources of heterogeneity or inconsistency.

Data management: Literatures: We use endnote and rayyan to filter and select intended RCTs. Data storage: Microsoft Excel 2021. Data analysis: Revman.

Quality assessment / Risk of bias analysis: To facilitate the assessment of possible risk of bias for each study, we will use the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) checklist tool specially designed to assess bias in safety meta-analyses. These judgements will be made independently by two review authors (SX, YCZ) based on the criteria for judging

the risk of bias. Disagreements will be resolved first by discussion and then by consulting a third author (MY) for arbitration. Neither of the review authors will be blind to the journal titles or to the study authors or institutions while assessing the risk of bias. Finally, quality of evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Strategy of data synthesis: Detailed adverse events table will be used to summarize the results of the included studies. The results of dichotomous outcomes will be presented as Peto Odds-ratio (in presence of rare events) with 95% Confidence Intervals will be calculated using fixed-effect model. We assessed between study heterogeneity using inconsistency index I^2 and χ^2 test with its p-value. Substantial between-study heterogeneity was defined as $I^2>50\%$, and significant heterogeneity was defined for a p-value<0.10. Data management, meta-analysis and meta-proportion analysis were performed with Review manager (version 5.4). A two-sided p-value<0·05 was considered statistically significant.

Subgroup analysis: Prespecified subgroup analyses were conducted according to prior systemic therapy, to the category of immune checkpoint inhibitors, to checkpoint inhibitors treatment setting, to checkpoint inhibitors assignation (alone or in combination with other therapy) and post-hoc analyses according to the median follow-up duration and, to the checkpoint inhibitors duration.

Sensitivity analysis: Prespecified sensitivity analyses of the primary outcome were computed to assess the robustness of results by recalculating the combined Peto OR: (i) with ClinicalTrials.gov data only and independently (ii) with published RCTs data only. If some of these studies had available data from both sources, we independently included each result reported in these two sensitivity analyses. Post-hoc secondary analyses were computed after removing trials with a sample size <100 patients/arm.

Language: English.

Country(ies) involved: China.

Other relevant information: N/A.

Keywords: Immune checkpoint inhibitors. sepsis. meta-analysis. randomized controlled trials.

Dissemination plans: It is not a intend meta analysis for dissemination plan, We are going to publish the review on completion.

Contributions of each author:

Author 1 - Miao Yan - Author 1 designed the protocol. He is responsible for resolving the disagreement during this meta analysis process, data analysis and bias assessment.
Email: yanmiao@csu.edu.cn
Author 2 - Shuang Xia - The author is responsible for literature searching and data extracting work.
Email: xiashuang@csu.edu.cn
Author 3 - Yichang Zhao - The author is responsible for literature searching and data extracting work.
Email: zhaoyichang@csu.edu.cn