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A systematic review of treatment-related adverse events for combination therapy of multiple tyrosine kinase inhibitor and immune checkpoint inhibitor

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ADMINISTRATIVE INFORMATION

Support - No funding.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - Takashi Sawada is an employee of MSD K.K. (a subsidiary of Merck & Co., Inc., Kenilworth, N.J., USA). however, employment in the company has not influenced the results and discussion presented in this paper. The other authors declare no competing interests.

INPLASY registration number: INPLASY202390011

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 September 2023 and was last updated on 05 September 2023.

INTRODUCTION

Review question / Objective The aim of this systematic review is to compare the combination of multiple tyrosine kinase inhibitors (multi-TKIs) plus immune checkpoint inhibitors (ICIs) and monotherapies of multi-TKIs in terms of safety profile. To this end, the proposed systematic review will address the following question: What is the effect of the addition of ICI to multi-TKIs on the profile of treatment-related adverse events.

Rationale Understanding the safety profile of this combination therapy is crucial for toxicity management. Few large-scale studies have investigated multi-TKI plus ICI combination therapy, which makes a comprehensive safety analysis difficult. In this study, we conduct a systemic review to examine the effect of adding ICI to multi-TKI on the safety profile.

Condition being studied In recent years, new anti-cancer drugs, molecular-targeted agents, and antibody drugs have been developed as replacements of conventional cytotoxic compounds. Also, various immunotherapies have been actively developed. Several clinical studies have been conducted on the use of ICIs in combination with other medications, including multi-TKIs for treating various cancers. Several ICIs (avelumab, pembrolizumab, and nivolumab) in combination with multi-TKIs (axitinib, lenvatinib, and cabozantinib) have been approved for the treatment of renal cell cancer.

METHODS

Search strategy We utilize PubMed and Web of Science using the terms PD-1, PD-L1, and inhibitor, and then the list was narrowed down using clinical trials. Second, to identify multi-TKIs that are used in combination with ICIs, the search is conducted using the generic names of the ICIs identified above and the term tyrosine kinase and the list is narrowed down using clinical trials. Finally, we search for clinical studies on multi-TKI monotherapy and combination therapy of multi-TKI and ICI using the generic names of the multi-TKIs identified above and narrowed down the list using clinical trials.

Participant or population This systemic review is based on patient population with various carcinomas in clinical studies regardless of whether they were single-arm or randomized clinical studies. Clinical studies in healthy volunteers, pediatric patients, and patients with hepatic disorders are excluded to minimize the impact of differences in the study populations.

Intervention Combination therapies of multi-TKIs (apatinib, axitinib, cabozantinib, lenvatinib, and regorafenib) plus anti PD-1/PD-L1 inhibitors (atezolizumab, avelumab, camrelizumab, durvalumab, nivolumab, and pembrolizumab).

Comparator Monotherapies of multi-TKIs (apatinib, axitinib, cabozantinib, lenvatinib, and regorafenib).

Study designs to be included This systematic review includes clinical trials to compare combination therapies of multi-TKIs (apatinib, axitinib, cabozantinib, lenvatinib, and regorafenib) in addition to anti PD-1/PD-L1 inhibitors (atezolizumab, avelumab, camrelizumab, durvalumab, nivolumab, and pembrolizumab) with a comparator of multi-TKIs monotherapies. In this study, the applicable clinical studies are included in the analysis regardless of whether they are single-arm or randomized clinical studies.

Eligibility criteria To evaluate the safety profile of multi-TKI and ICI combination therapy, the following criteriaare applied to select clinical studies to be evaluated in this study: (i) published clinical studies on multi-TKI monotherapy and those on multi-TKI plus ICI combination therapy that reported treatment-related adverse events (incidence ≥10%). (ii) For each of the selected clinical studies, the following common adverse events are selected for this study with reference to the package insert of multi-TKIs: anorexia, constipation, weight loss, diarrhea, fatigue, hand-foot syndrome (including palmar-plantar erythrodysesthesia syndrome), hypertension, hypothyroidism, nausea, proteinuria, rash, and vomiting. (iii) For each adverse event, the number of events is extracted from the clinical studies on multi-TKI monotherapy and multi-TKI plus ICI combination therapy.

Information sources As a primary data source, we utilize PubMed (https://pubmed.ncbi.nlm.nih.gov/). We also use Web of Science (https://www.webofscience.com/wos) as a secondary data source and searched for clinical trials.

Main outcome(s) The primary endpoint is the relative risk (RR) for the combination therapy of multi-TKIs and ICIs compared with sunitinib. For each of the selected adverse events, the relative risk (RR) for the combination therapy of multi-TKIs and ICIs compared with sunitinib is calculated. We also identify the trials by ClinicalTrials.gov identification number (i.e., NCT number), first author and the year of publication, and extract the following information from the reports: intervention of experimental treatment, number of subjects, study phase, and tumor type/disease condition.
In addition, another primary endpoint is comparison of adverse events between multi-TKI monotherapy and multi-TKI plus ICI combination therapy. For each of the selected adverse events, the numbers of studies with ≥10% incidence and those with <10% incidence are counted separately for multi-TKI monotherapy and multi-TKI plus ICI combination therapy.

Additional outcome(s) The pooled incidence rate for the selected adverse events is calculated separately for multi-TKI monotherapy and multi-TKI plus ICI combination therapy as reference.

Data management Two independent reviewers (TS and MN) screen the names and designs of the clinical trials for the records derived from PubMed and Web of Science, followed by assessment of eligibility based on the full texts. Disagreements about eligibility are resolved through discussion. A single reviewer (TS) performs the initial data extraction using a standardized data collection form and second reviewer (MN) carefully checks them. Discrepancies are resolved through a discussion between them. The meta-analysis is performed using StatsDirect (Stats-Direct Ltd., Cheshire, UK).

Quality assessment / Risk of bias analysis The quality and risk of bias of randomized controlled trials (RCTs) are assessed with the revised

Cochrane Collaboration's risk of bias tool (Rob 2.0). We follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for the purpose of this analysis.

Strategy of data synthesis The systemic review is performed using StatsDirect (Stats-Direct Ltd., Cheshire, UK). The analyses are performed using a random effects model because studies are expected to be different (e.g., multiple cancer types) and treatment regimens are not identical among studies. Analyses are conducted for the followings: (i) the relative risk (RR) for the combination therapy of multi-TKIs and ICIs compared with sunitinib. (ii) For each of the selected adverse events, the numbers of studies with ≥10% incidence and those with <10% incidence are counted separately for multi-TKI monotherapy and multi-TKI plus ICI combination therapy. Fisher's exact test is used to examine whether there is an imbalance in the number of studies between multi-TKI monotherapy and multi-TKI plus ICI combination therapy. (iii) The pooled incidence rate and its 95% confidence interval for the selected adverse events are calculated separately for multi-TKI monotherapy and multi-TKI plus ICI combination therapy.

Subgroup analysis Subgroup analyses will not be performed in this study.

Sensitivity analysis If heterogeneity exists, continue with sensitivity analysis after excluding heterogeneity.

Language restriction Only clinical trials published in English are considered for inclusion.

Country(ies) involved Japan.

Keywords Systematic review, multiple tyrosine kinase inhibitor, immune checkpoint inhibitor, treatment-related adverse events, PD-1/PD-L1 inhibitor.

Dissemination plans Publication in a peer-review journal.

Contributions of each author

Author 1 - Takashi Sawada - conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing-original draft, writing-editing.
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