INPLASY PROTOCOL

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None declared.

Survival Benefits and Bleeding Risk of Anti-VEGF Agents for Renal Cell Carcinoma (RCC): A Updated Systematic Review and Meta-Analysis of Phase 2 and 3 Randomized Clinical Trials

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Review question / Objective: **To investigate the survival benefits (PFS, DFS, OS) and bleeding risk of the anti-VEGF agents compared with placebo or interferon alpha (IFNa) in patients with RCC.**
Condition being studied: **Part 1. The hazard ratio (HR) of the progression-free survival (PFS) and overall survival (OS) of anti-VEGF agents vs. non/placebo for patients with unresectable, advanced, metastatic, renal cell carcinoma (RCC).**
Part 2. The HR of the disease-free survival (PFS) and OS of anti-VEGF agents vs. non/placebo for patients with post-nephrectomy RCC (adjuvant use).
Part 3. The HR of the PFS and OS of anti-VEGF agents vs. IFN-alpha for patients with RCC.
Part 4. The relative risk (RR) of bleeding events of anti-VEGF agents vs. placebo or IFN-alpha for patients with RCC.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 March 2023 and was last updated on 03 March 2023 (registration number INPLASY202330007).

INTRODUCTION

Review question / Objective: **To investigate the survival benefits (PFS, DFS, OS) and bleeding risk of the anti-VEGF agents compared with placebo or interferon alpha (IFNa) in patients with RCC.**

Rationale: **Agents targeting vascular endothelial growth factor (VEGF, either the ligands, receptors, receptor tyrosine kinases, or downstream signal pathways) are the major treatment of unresectable, advanced, metastatic, and recurrent RCC, according to clinical practice guideline from European Society of Medical**

Oncology (ESMO) and American Society of Clinical Oncology (ASCO).

The most recent meta-analysis conducted by Iacovelli et al. in 2015 revealed that agents targeting VEGF/VEGFR pathway significantly improve the progression free survival (PFS) and overall survival (OS) among patients with metastatic RCC.

The efficacy of adjuvant use of anti-VEGF agents in localized or locally-advanced RCC have also been investigated by Sun et al., and their meta-analysis obtained from 3 phase 3 randomized clinical trials (RCT) denoted no benefits of disease-free survival (DFS) of the anti-VEGF agents for post-nephrectomy RCC patients .

Hofmann et al. concluded that the PFS and OS of combined regimens including immune checkpoint inhibitors (ICI) and VEGF TKI are superior to single-agent targeted therapy in patients with RCC.

In this updated meta-analysis, we focus on the survival benefits and the bleeding events of anti-VEGF agents (including monoclonal antibodies, TKIs, and mTOR inhibitors) versus placebo or interferon alpha (IFNα).

Condition being studied: Part 1. The hazard ratio (HR) of the progression-free survival (PFS) and overall survival (OS) of anti-VEGF agents vs. non/placebo for patients with unresectable, advanced, metastatic, renal cell carcinoma (RCC).

Part 2. The HR of the disease-free survival (PFS) and OS of anti-VEGF agents vs. non/placebo for patients with post-nephrectomy RCC (adjuvant use).

Part 3. The HR of the PFS and OS of anti-VEGF agents vs. IFN-alpha for patients with RCC.

Part 4. The relative risk (RR) of bleeding events of anti-VEGF agents vs. placebo or IFN-alpha for patients with RCC.

METHODS

Search strategy: Via databases including MEDLINE/Pubmed, Embase, and Cochrane Library, we used the searching strategy of following keywords: ("renal cell carcinoma" OR "renal cancer" OR RCC) AND (axitinib OR bevacizumab OR cabozantinib OR everolimus OR lenvatinib OR pazopanib OR sorafenib OR sunitinib OR temsirolimus OR tivozanib OR "anti-VEGF"), and the MeSH terms of RCC and anti-VEGF agents are utilized as well.

The filters used in the database are shown below: MEDLINE/Pubmed with filters of "clinical trial" and "randomized clinical trial"; Embase with filters of "randomized clinical trial", "phase 3 clinical trial", "phase 2 clinical trial", and "article"; and Cochrane Library with "clinical trials". The literature search was done on February 25th, 2023.

We also took advantage of the ClinicalTrials.gov to discover the research additionally for better exploration of the potential trials.

Participant or population: Patients with RCC in different status: localized or locally advanced (post-nephrectomy, adjuvant use of anti-VEGF agents), advanced, and metastatic.

Intervention: Anti-VEGF agents: axitinib, bevacizumab, cabozantinib, everolimus, lenvatinib, pazopanib, sorafenib, sunitinib, temsirolimus, tivozanib, and other.

Comparator: Placebo or non (e.g., observation); interferon alpha-2a.

Study designs to be included: Phase 2 and phase 3 randomized clinical trials (RCT).

Eligibility criteria: Inclusion criteria: (1) anti-VEGF vs. placebo or non (e.g., observation), (2) anti-VEGF X + anti-VEGF Y vs. anti-VEGF X, (3) random agents or intervention (e.g., IFN alpha-2a) + anti-VEGF vs. random agents or intervention ± placebo, and (4) anti-VEGF with active titration vs. anti-VEGF with placebo titration; the comparison arms of anti-VEGF vs. IFN alpha-2a following the principles above are also selected.

Information sources: MEDLINE/Pubmed, Embase, and Cochrane Library are utilized. No authors is contacted for detailed data. ClinicalTrials.gov is used for data extraction of the included studies. No grey literature is included in the study.

Main outcome(s): Progression-free survival, disease-free survival, overall survival, hazard ratio of disease progression and death, and all bleeding events.

Data management: We extracted the following data from the included studies: first author, year of publish, trial name, NCT registration number from ClinicalTrials.gov, RCT phase, masking condition, status of patients and RCC, treatment line, total number of recruited patients and each treatment groups, intervention arm, and comparison arm.
The data of PFS, DFS, OS, and hazard ratio (HR) are obtained from the ClinicalTrials.gov if available (otherwise, in the article and their updated or final reports), and the bleeding events are obtained from the "Adverse Events" section in the ClinicalTrials.gov or in the articles.

Quality assessment / Risk of bias analysis: The study qualities of the included RCTs were assessed via Cochrane risk-of-bias tool version 2.0 (RoB 2) for randomized trials, including the bias of randomization process, deviations from the intended interventions, missing outcome data, outcome measurement, selection of the reported result, and the overall risk of bias.
The results of each section and overall assessment are displayed in 3 categories: low risk, some concerns, and high risk.

Strategy of data synthesis: The meta-analyses were conducted using Review Manager 5 (RevMan 5) version 4.1 (Cochrane, 11-13 Cavendish Square, London W1G 0AN, United Kingdom) and were demonstrated by forest plots.
The HR of survival benefits (by formats of generic inverse variance outcome) and the risk ratio (RR) of bleeding events with 95% confidence interval (CI) between the intervention and comparison arms are calculated. A two-tailed p value of less than 0.05 was considered statistically significant.
The meta-analyses of survival benefits are separated by 3 parts: PFS/OS of anti-VEGF vs non/placebo in advanced RCC, DFS/OS of adjuvant use of anti-VEGF vs. comparator, and PFS/OS of anti-VEGF vs. IFN.

Subgroup analysis: The analysis of bleeding risk is further adjusted by excluding hematuria events and inclusion of serious-only bleeding events; subgroup analyses regarding bleeding risk of different classes of anti-VEGF agents are also conducted.

Sensitivity analysis: The sensitivity analysis is conducted across the risk-of-bias assessments and outlier data of the trials if needed.

Language restriction: English-only.

Country(ies) involved: Taiwan (Republic of China, ROC).

Keywords: renal cell carcinoma (RCC); vascular endothelial growth factor (VEGF); anti-VEGF agents; survival benefits; systematic review; meta-analysis.

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