

Adjuvant targeted therapy combined with surgery for advanced and metastatic renal cell carcinoma

A protocol for systematic review and meta analysis

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Abstract

Background: The aim of this systematic review and meta-analysis is to evaluate the efficacy and safety of adjuvant targeted therapy by sunitinib combined with surgery in the treatment of advanced or metastatic renal cell carcinoma.

Methods: PubMed/Medline, Web of Science, Cochrane Library, ClinicalTrials.gov (<http://www.ClinicalTrials.gov>), China National Knowledge Infrastructure (CNKI) will be searched for clinical research articles related to the efficacy and safety of adjuvant therapy combined with surgery in the treatment of advanced and metastatic RCC. The identification, inclusion and exclusion flow charts will be conducted according to the PRISMA guidelines. The quality assessment will be done by Quadas-2 evaluation tool. Key parameters including OS in 10, 20, 30, and 40 months, PFS in 10, 20, and 30 months, objective response rate (ORR), stable disease (SD) rate, progressive disease (PD) rate, median OS and PFS, types of AEs and their occurrence rates, etc will be extracted. The evaluation of the efficacy and safety will be pooled by CMA.

Results: This systematic review will provide evidence on the efficacy and safety of adjuvant therapy by sunitinib combined with surgery in treating advanced and metastatic RCC.

Conclusion: The study aims to generalize data concerning the response rate, OS, PFS and rates of adverse effects of the perioperative use of sunitinib in advanced and metastatic RCC patients. The evidence provided by this systematic review and meta-analysis will help guide the clinical decision making and enlighten the future management of advanced or metastatic RCC.

Registration: This protocol has been registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY registration number: INPLASY2020110093; INPLASY DOI number: 10.37766/inplasy2020.11.0093 Available at: <https://inplasy.com>).

Abbreviations: AE = adverse effect, CMA = comprehensive meta-analysis, CNKI = China National Knowledge Infrastructure, ORR = objective response rate, OS = overall survival, PD = progressive disease, PFS = progression free survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols, RCC = renal cell carcinoma, SD = stable disease, TKI = tyrosine kinase inhibitor, VEGFR = vascular endothelial growth factor receptors.

Keywords: adverse effects, efficacy, perioperative use of sunitinib, safety

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Renal cell carcinoma (RCC) is one of the most common malignancies of the genitourinary tract originating from the cells in proximal convoluted tubule.^[1,2] Accordingly, the global mortality nearly doubled in 15 years from 1985 to 2000.^[3,4] Clinically, the majority of patients are asymptomatic during the early stages of RCC, thus only a fraction of patients is efficiently diagnosed and subsequently managed.^[5] Due to the rapid progress and high invasiveness of RCC, patients who are only correctly managed during late stage have a comparatively low possibility of complete recovery.^[6,7]

One of the most important factors contributing to the rapid development and invasiveness is its tendency of metastasis.^[8] Specifically, direct metastasis into the peritoneal cavity, migration into the blood vessels and even formation of large-sized venous thrombus into the right atrial system are common pathways for disease progress.^[9,10] Usually, the appearance of venous thrombus in the right atrial system marks the turning point for the escalation of disease severity.^[11] Despite knowing the rigorous fact, solutions to effectively remove the lesions are still limited. Currently, surgery is the first choice for patients diagnosed with

advanced conditions like this for it directly removes both the original tumor and the metastatic thrombus.^[12] Nevertheless, radical surgeries often involve sternotomy and optional cardiac arrest, which are challenging. As a result, adjuvant drug therapy has increasingly been adopted to aid surgical process or to directly treat patients.^[13,14]

Sunitinib is a tyrosine kinase inhibitor (TKI) which is usually used in adjuvant targeted therapy.^[15] It can inhibit several receptors which have an effect in tumorigenesis and tumor progress of RCC, including vascular endothelial growth factor receptors (VEGFRs, like VEGFR-1, VEGFR-2, VEGFR-3) and c-Kit.^[16,17] Angiogenesis is mandatory in the progression of RCC since it provides tumor tissues with adequate oxygen and nutrients. Thus, combined use of TKIs which helps to restrict the emerging of blood vessels is believed to play a role in managing RCC.

Up to now, several important clinical trials have been carried out worldwide to evaluate the efficacy and safety of the aforementioned combined adjuvant targeted therapy and surgery. Some studies including 2 famous landmark trials have pointed out that this combined therapy could degrade tumor stage and halt tumor development and reduce the size of both the original tumor and metastatic neoplasms.^[18,19] However, there exist other reports claiming that such combination had no direct impact on tumor growth and on the contrary would bring other drug safety concerns such as provoking several adverse effects. These mainly included hand and foot syndrome, malaise, digestive problems, etc. Besides, many of these studies are single-arm trials or fail to recruit sufficient number of patients. Therefore, the present study will synthesize the results of current available evidences to assess the efficacy and safety of the combined therapy of surgery and adjuvant targeted therapy in patients with advanced or metastatic RCC.

2. Material and methods

This protocol has been registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY registration number: INPLASY2020110093; INPLASY DOI number: 10.37766/inplasy2020.11.0093 Available at: <https://inplasy.com>). This protocol will be conducted according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P). This study has been approved by the Ethics Committee of West China Hospital, Sichuan University (Chengdu China).

2.1. Search strategy

Following PRISMA-P, we will carefully search authenticated databases including PubMed/Medline, Web of Science, Cochrane Library, ClinicalTrials.gov (<http://www.ClinicalTrials.gov>), China National Knowledge Infrastructure (CNKI) for clinical research articles related to the efficacy and safety of adjuvant therapy combined with surgery in the treatment of advanced and metastatic RCC. In order to study the latest articles, we will only include articles published between January 2008 and May 2020.

2.2. Article selection

We will assign 3 independent reviewers to judge duplicates and relevancy, in which obvious duplicates and irrelevant articles will be excluded from further analysis. Remaining articles will be interrogated to extract full texts and raw data. In this process, case reports, reviews, letters and meeting proceedings will be excluded.

The inclusion criteria will include: first, reported at least either indicators for survival analysis or data concerning the AEs; and second, randomized controlled trials and any observational design, including cross-sectional, case-control, and cohort designs.

The consensus on the article selection process will be reported and more independent reviewers will be consulted if discrepancy should occur.

2.3. Data extraction

After selecting qualified articles, we will extract important information from these articles. The information will mainly include the basic details of the articles, patients demographic characteristics, data concerning the efficacy and safety. More specifically, key parameters will include OS in 10, 20, 30, and 40 months, PFS in 10, 20, and 30 months, objective response rate (ORR), stable disease (SD) rate, progressive disease (PD) rate, median OS and PFS, types of AEs and their occurrence rates, etc. The baseline characteristics of the articles will include title, first author, nationality, department, study design and enrollment year. Finally, sex and median age, ethnicity of the patients will also be carefully extracted as the demographic features.

2.4. Quality assessment

We will perform standard quality assessment of the included studies based on Quadas-2 tool. By Quadas-2, the articles will be evaluated in the following processes: sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and others.

2.5. Publication bias

To avoid publication bias, if over 10 articles will be included to extract qualified data for further analysis, we will apply the “funnel plot” to detect the potential risk of publication bias. If not, we will implement Begg test and Egger test. All the aforementioned tests will be performed through Stata 14.2 (Stata Corp).

2.6. Heterogeneity assessment

We will apply I^2 statistics and Galbraith plot method to evaluate the heterogeneity. If $I^2 < 50\%$, we will use a fixed-effects model. If we come across a high heterogeneity, we will use the Galbraith plot to identify the outliers and thus perform a sensitivity analysis.

2.7. Statistical analysis

The occurrence rate of AEs, including AEs of all grades and of grade ≥ 3 AEs as well as their 95% confidential interval (CIs) will be calculated based on data collected from these single-arm trials. All the analyses and calculations mentioned above will be conducted using comprehensive meta-analysis (CMA) (Biostat, Englewood, NJ).

3. Discussion

Advanced and metastatic RCC is a common type of malignancy of the kidney which easily leads to life-threatening events. The first-line treatment of advanced and metastatic RCC is radical

surgery, despite that the surgery itself has quite a high degree of risk.^[20] To provide better prognostic opportunity, physicians have brought up the concept of combined adjuvant therapy by sunitinib. Although a series of studies proved that adjuvant therapy by sunitinib was beneficial in that it was able to decrease tumor size and prevent continuous production of tumor thrombus.^[21] However, there were indeed some other studies providing the opposite conclusions. This systematic review and meta-analysis will objectively report the efficacy of sunitinib based on large data analysis.^[22]

Besides the efficacy, the safety concerns of sunitinib were also heatedly discussed. So far, previous articles have claimed that proteinuria, anemia, asthenia, pause syndromes, etc were the most common AEs. Through systematic review and meta-analysis, we will provide the general pooled occurrence rate of all-grade AEs and grade \geq 3 AEs in order to enlighten the safety concerns of sunitinib.

Author contributions

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