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First-line Systemic Therapy for Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis

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Abstract

Context: In the last decade, there has been a proliferation of treatment options for metastatic renal cell carcinoma (mRCC). However, direct comparative data are lacking for most of these agents.
Objective: To indirectly compare the efficacy and safety of systemic therapies used in the first-line treatment of mRCC.
Evidence acquisition: Medline, EMBASE, Web of Science, and Scopus databases were searched using the OvidSP platform for studies indexed from database inception to October 23, 2017. Abstracts of conferences of relevant medical societies were included, and the systematic search was supplemented by hand search. For the systematic review, we identified any parallel-group randomized controlled trials assessing first-line systemic therapy. For network meta-analysis, we limited these to a clinically-relevant network based on standard practice patterns. Progression-free survival (PFS) was the primary outcome. Overall survival (OS) and grade 3 and 4 adverse events (AEs) were secondary outcomes.
Evidence synthesis: In total, 37 trials reporting on 13 128 patients were included in the systematic review. The network meta-analysis comprised 10 trials reporting on 4819 patients. For PFS (10 trials, 4819 patients), there was a high likelihood (SUCRA 91%) that cabozantinib was the preferred treatment. For OS (5 trials, 3379 patients), there was a 48% chance that nivolumab plus ipilimumab was the preferred option. There was a 67% likelihood that nivolumab plus ipilimumab was the best tolerated regime with respect to AEs.
Conclusions: Cabozantinib and nivolumab plus ipilimumab are likely to be the preferred first-line agents for treating mRCC; however, direct comparative studies are warranted. These findings may provide guidance to patients and clinicians when making treatment decisions and may help inform future direct comparative trials.
Patient summary: There are many treatment options for patients diagnosed with metastatic renal cell carcinoma. We indirectly compared the available options and found that cabozantinib and nivolumab plus ipilimumab are likely to be preferable choices as the first-line treatment in this situation.

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1. Introduction

Kidney cancer is the 6th most common malignancy among men and 10th among women, accounting for an estimated 65 340 new cases and nearly 15 000 mortalities in 2018 in the United States [1]. Furthermore, 25–30% of patients present with metastases at the time of diagnosis [2]. Historically, treatment for metastatic RCC (mRCC) had been limited to cytokine therapies (interleukin-2 and interferon-alfa). However, the development of tyrosine kinase inhibitors (TKIs), which target vascular endothelial growth factors, and mammalian target of rapamycin (mTOR) inhibitors has superseded cytokine-based therapies, which have greater toxicity and relatively lower efficacy. More recently, checkpoint inhibitors have introduced a further therapeutic option.

Currently, there are eight first-line therapies approved for patients with mRCC, including the recent Food and Drug Administration (FDA) approval of cabozantinib, a multi-kinase inhibitor [3]. Furthermore, two recently completed phase III studies have propelled immunotherapy options into the first-line therapy space: CheckMate 214 demonstrated an overall survival (OS) benefit for first-line nivolumab plus ipilimumab versus sunitinib [4], and IMmotion151 reported a progression-free survival (PFS) benefit for first-line atezolizumab plus bevacizumab versus sunitinib [5]. However, limited direct comparative data exist between these agents to be able to inform treatment decisions, guideline recommendations [6], and clinical trial design. As such, we undertook a systematic review of all clinical trials assessing first-line systemic therapy of mRCC and employed network meta-analyses to perform indirect comparisons of efficacy and safety outcomes.

2. Evidence acquisition

2.1. Methodology

We performed a systematic review and network meta-analysis of parallel-group randomized controlled trials (RCTs) which compared two systemic therapies in the first-line treatment of mRCC. RCTs were included regardless of the follow-up duration. No limitations were placed with respect to publication year. Only English language publications were considered, though this has not been shown to bias meta-analysis estimates previously [7]. Observational studies, editorials, commentaries, review articles, and those not subject to peer-review (ie, reports of data from Vital Statistics and dissertations or theses) were excluded. Bibliographies of included studies were hand-searched to ensure completeness. Abstracts of meetings of relevant medical societies (up to and including the 2018 American Society of Clinical Oncology Genitourinary Cancers Symposium) were searched to compliment the systematic review. Following the literature search, all duplicates were excluded.

As we were interested in the efficacy of these agents in the first-line treatment of patients who had not previously received systemic therapy, studies in which patients had previously received systemic therapy or in which this subset could not be excluded from the overall cohort for the purposes of analysis were excluded.

In instances where there was more than one publication resulting from the same patient cohort and reporting the same outcome, we utilized the most recent publication for analysis. Where two publications utilizing the same cohort reported on different outcomes, each was included. We conducted and reported this review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [8].

2.2. Outcome measures

The primary outcome was PFS, as reported by study authors. Secondary outcomes were investigator-reported OS and rates of grade 3 or 4 adverse events (AEs).

2.3. Search strategy

Medline, EMBASE, Web of Science, and Scopus databases were searched using the OvidSP platform for studies indexed from database inception to October 23, 2017 by a professional librarian. We used both subject headings and text-word terms for “metastatic”, “renal cell carcinoma”, “chemotherapy”, “immunotherapy”, “targeted systemic therapy”, “progression-free survival”, “survival”, and related and exploded terms including MeSH terms in combination with keyword searching. These results were restricted to RCTs. A full search strategy is presented in Appendix 1. References from review articles, commentaries, editorials, included studies, and conference publications of relevant medical societies were hand-searched and cross-referenced to ensure completeness. Conference abstracts were included where they reported data that was not available from published manuscripts.

2.4. Study review methodology

Two authors performed study selection independently (C.J.D.W. and Z.K.). Disagreements were resolved by consensus. Titles and abstracts were used to screen for initial study inclusion. Full-text review was used where abstracts were insufficient to determine if the study met inclusion criteria. One author (Z.K.) performed all data abstraction with independent verification performed by another author (C.J.D.W.).

2.5. Risk of bias assessment

A risk of bias assessment was conducted using The Cochrane Collaboration's tool for assessing risk of bias [9]. This tool assesses selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and other sources of bias.

2.6. Data synthesis

The available direct comparisons between agents were illustrated using a network diagram for each outcome.

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