Editorial

The power of meta-analysis in therapeutic decision making for advanced kidney cancer

Ulka Vaishampayan

Department of Oncology, Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA
Correspondence to: Ulka Vaishampayan, MD. Department of Oncology, Karmanos Cancer Institute/Wayne State University, 4100 John R, Detroit, MI 48201, USA. Email: vaishamu@karmanos.org.
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Introduction

Despite being a relatively uncommon cancer, kidney cancer has made tremendous advances over the past two decades. In fact, it has served as the blueprint for proof of principle of various targeted and immune therapies. A plethora of clinical trials have been reported and completed in this disease within the last decade. The results have led to a paradigm shift in the management approach towards renal cell carcinoma (RCC). Multiple complicated factors need to be considered during the decisions regarding systemic therapy, along with the interplay of sequencing with local therapies. The paper by Wallis *et al.* (1) focuses on the current treatment dilemma of front line therapy options in patients with newly diagnosed metastatic or advanced kidney cancer. A meta-analysis of the data from the randomized trials comparing front line systemic therapies, conducted in this disease state, form the subject matter of the paper. The study is an attempt to simplify therapeutic choices with evaluating a large body of evidence and condensing it into crystallized evidence-based recommendations. The analysis spans a patient experience of 13,128 cases of untreated advanced RCC enrolled across 37 clinical trials.

Goals of a meta-analysis are to pool results of separate but similar experiments to test the validity of the conclusions and provide an additional tool for the pursuit of evidence-based medicine in practice. Meta-analysis is a quantitative, formal, epidemiological study design used to systematically assess previous research studies to derive conclusions about that body of research (2). Combining multiple trials to expand effective sample size enables the derivation of a single conclusion with greater statistical power. Outcomes from a meta-analysis may include a more precise estimate of the effect of treatment or risk factor for disease, or other outcomes, than any individual study contributing to the pooled analysis. In summary meta-analysis adds value to the knowledge base regarding a focused patient population. It is also useful in clarifying risk benefit ratio of therapeutic agents. However, it is rarely practice changing and typically will not impact standard of care.

Interpretation of meta-analysis results

This study carefully selected 37 randomized trials comparing distinct systemic therapy agents that represented contemporary therapies. Trials including outdated therapies such as interferon alfa were excluded, and clinically current and relevant therapies such as targeted therapies and immune therapies were included. The selection bias inherent to any meta-analysis is that the study selection is weighted towards positive result trials. Negative results trials are less likely to be published and hence are frequently not captured in meta-analyses.

The meta-analysis had 4 main conclusions: (I) for the progression free survival (PFS) endpoint in front line therapy of RCC, cabozantinib demonstrated superior efficacy; (II) for overall survival (OS), ipilimumab and nivolumab was in the forefront; (III) ipilimumab and nivolumab combination had the least likelihood of serious adverse events in comparison to the tyrosine kinase inhibitors (TKI); (IV) within intermediate and high risk International Metastatic Disease Consortium (IMDC) subgroup of RCC,

cabozantinib emerged as the preferred therapeutic choice for optimal PFS outcome and ipilimumab and nivolumab was the preferred choice for OS outcome.

Application of results

The meta-analysis revealed that two distinct therapeutic regimens were favored for PFS and OS. It is reassuring that the results were consistent with those noted in the index registration trials of each agent/s; CABOSUN (3) and Checkmate 214 (4), that led to Food and Drug Administration (FDA) approval of these regimens. However, the results create a somewhat frustrating dilemma and require the clinician to choose between PFS and OS as the preferred outcome when selecting appropriate therapy for frontline advanced RCC. Ideally, PFS is expected to be a consistent surrogate for OS, however this endpoint can be confounded with subsequent therapies which are not captured in most clinical trials. However, OS remains the gold standard and every medical provider is usually treating patients with the goal of achieving a longer life span for their patient. In addition, response rates and quality of life parameters were not evaluated and maybe worthy of future investigation.

Currently the therapy of renal cancer is in a state of flux. A variety of treatment regimens are rapidly outpacing the existing regimens, in multiple clinical trials that have been conducted in parallel. Recently a regimen of axitinib and avelumab reported superior PFS results in comparison to sunitinib in frontline therapy of RCC (5). The results of this JAVELIN 101 trial showed that PFS was significantly improved with axitinib and avelumab with median PFS of 13.8 months as compared to 8.4 months with sunitinib monotherapy [hazard ratio (HR) =0.69, P=0.0001]. In addition, the randomized trial comparing axitinib and pembrolizumab with sunitinib, also reported that the interim analysis met the prespecified endpoint of improved PFS and OS with the combination regimen (6). The phenomenon of a plethora of trials with regimens showing superiority over sunitinib, has resulted in a complicated therapeutic landscape. None of these regimens have been compared to each other hence adding to the challenge of therapeutic decision making. It is also clear that a new control will need to be determined for future study design, but it remains unclear at present which of these regimens should be considered to fulfill the role of future "standard arm". The value of the current meta-analysis could be to recommend the utilization of cabozantinib as the future control arm for studies with PFS as the primary endpoint

and the choice of ipilimumab and nivolumab as the control arm for studies with OS as the primary endpoint (*Table 1*). Establishing a benchmark control arm for response rate should also be considered and is especially important for phase II evaluation of novel agents in advanced RCC. With regards to toxicity and risk benefit ratio determination, the regimen of ipilimumab and nivolumab appears to be the best tolerated and is comparable with the regimen of atezolizumab and bevacizumab. Future regimens will likely have to utilize these regimens as benchmarks for toxicity comparisons.

Kidney cancer is a heterogenous disease and even within the widely used clinical risk categorization, the spectrum of median OS ranges from 48 months in the favorable risk group to 9 months in the poor risk group (7). The current meta-analysis evaluates for the intermediate/poor risk group but does not explore other biomarkers that may impact patient prognosis within RCC. Some of these would include programmed death ligand expression (PD-L1) and histology of clear versus non-clear cell, the impact of cytoreductive nephrectomy and the presence of patient comorbidities. The examination of variability or heterogeneity in study results is also a critical outcome and needs to be addressed in meta-analyses. The patient population that is underrepresented in clinical trials (*Table 2*) should also be the topic of more detailed investigation to integrate findings from multiple studies in a rigorously conducted meta-analysis.

Summary and conclusions

The meta-analysis has strengthened the recommendations for considering the front-line therapies of cabozantinib, and ipilimumab and nivolumab, in untreated advanced RCC. The results were consistent with the data from the index registration trials and add value by broadening the scope of the experience, and enhancing the power of the conclusions. Another critical contribution of the meta-analysis is that it has imparted potential control arms for future clinical trial design.

Acknowledgments

Footnote

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Table 1 Interpretation of meta-analysis

Endpoint	Preferred agent/regimen
PFS in frontline therapy of RCC	Cabozantinib
OS in frontline therapy of RCC	Ipilimumab + nivolumab
Toxicity	Ipilimumab + nivolumab
PFS in intermediate/high risk group	Cabozantinib
OS in intermediate/high risk group	Ipilimumab + nivolumab
Future study design control arm: PFS as primary endpoint	Cabozantinib
Future study design control arm: OS as primary endpoint	Ipilimumab + nivolumab

RCC, renal cell carcinoma; OS, overall survival; PFS, progression free survival.

Table 2 Factors likely to impact conclusions of meta-analysis

Publication bias: negative trial data is not incorporated
The index trials contributed majority of the patients
Toxicity analysis: quality of life and patient reported outcomes were not included
Results impacted by the choice of primary endpoints for the index trials
Response rates were not evaluated
Patient populations underrepresented in clinical trials not studied:
Patient without cytoreductive nephrectomy
Patients with autoimmune disease or immunocompromise, as they do not qualify for most immune based regimen trials
Brain metastases
Organ dysfunction: patients with liver, cardiac, renal dysfunction

and reviewed by the Section Editor Peng Zhang, MD, PhD (Department of Urology, Zhongnan Hospital of Wuhan University, Wuhan, China).

Ethical statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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