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European Association of Urology

Platinum Priority – Collaborative Review – Kidney Cancer

Editorial by Dae Y. Kim and Jose A. Karam on pp. 111–113 of this issue

A Systematic Review of Sequencing and Combinations of Systemic Therapy in Metastatic Renal Cancer

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Article info

Article history:
Accepted April 13, 2014

Keywords:
Renal cell carcinoma
Tyrosine kinase inhibitor
Sequence of systemic therapies
Combination of systemic therapies

Abstract

Context: The introduction of novel molecular-targeted agents has revolutionised the management of patients with metastatic renal cell carcinoma (mRCC). However, uncertainties remain over sequential or simultaneous combination therapies.
Objective: To systematically review relevant literature comparing the clinical effectiveness and harms of different sequencing and combinations of systemic targeted therapies for mRCC.
Evidence acquisition: Relevant databases (including Medline, Cochrane Library, trial registries, and conference proceedings) were searched (January 2000 to September 2013) including only randomised controlled trials (RCTs). Risk of bias assessment was performed. A qualitative and quantitative synthesis of the evidence was presented.
Evidence synthesis: The literature search identified 5149 articles. A total of 24 studies reporting on 9589 patients were eligible for inclusion; data from four studies were included for meta-analysis. There were generally low risks of bias across studies; however, clinical and methodological heterogeneity prevented pooling of data for most studies. Overall, the data showed several targeted therapies were associated with an improvement in progression-free survival in patients with mRCC. There were limited data from RCTs regarding the issue of sequencing; studies on combination therapies have been hampered by difficulties with tolerability and safety.
Conclusions: Although the role of vascular endothelial growth factor/vascular endothelial growth factor receptor targeting therapies and mammalian target of rapamycin inhibition in the management of mRCC is now established, limited reliable data are available regarding sequencing and combination therapies. Although data from retrospective cohort studies suggest a potential benefit for sequencing systemic therapies, significant uncertainties remain. Presently, mRCC systemic treatment should follow international guidelines (such as the European Society for Medical Oncology, National Comprehensive Cancer Network, and European Association of Urology) for patients fit to receive several lines of systemic therapies.
Patient summary: We thoroughly examined the literature on the benefits and harms of combining drugs for the treatment of kidney cancer that has spread and on the sequence in which the drugs should be given.

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http://dx.doi.org/10.1016/j.eururo.2014.04.006
0302-2838/

1. Introduction

The introduction of seven new agents in the past 8 yr has transformed systemic treatment of metastatic renal cell carcinoma (mRCC), improving prognosis from a median overall survival (OS) of approximately 1 yr to >2 yr [1]: four multitargeted tyrosine kinase inhibitors (TKIs): sorafenib [2], sunitinib, pazopanib [3], and axitinib [4]; the humanised antivascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab with interferon (IFN)-α2a [5], and two mammalian target of rapamycin (mTOR) complex 1 kinase inhibitors (temsirolimus [6] and everolimus [7]).

Only two classes of agents are used in clinical practice inhibiting either the VEGF/VEGF receptor (VEGFR) axis or mTOR. Unlike bevacizumab that can selectively inhibit VEGF (ligand of VEGFRs), the commonly used TKIs interfere with several growth factor receptors in addition to VEGFRs. Thus sunitinib and pazopanib inhibit predominantly VEGFRs and platelet-derived growth factor receptor (PDGFR), and c-Kit, whereas sunitinib may also target Flt-3. Sorafenib inhibits VEGFRs, PDGFR, c-Kit, Flt-3, and the serine-threonine kinase Raf-1. Axitinib exhibits higher affinity and higher selectivity for VEGFRs. The mTOR complex is upstream of intracellular pathways regulating key transcription factors involved in cellular survival, proliferation, metabolism, and angiogenesis, and it is critical in the pathogenesis of mRCC [8].

Despite several years of unprecedented single-agent activity with these novel drugs, the response rate (RR), progression-free survival (PFS), and OS observed in single-agent randomised controlled clinical trials (RCTs) have finally reached a plateau. Therefore, strategies have focussed on optimal sequencing and combinations of existing agents to maximise their impact on clinical outcomes. In addition, new therapeutic targets are being actively explored.

We performed a systematic review to determine if the available data support combinations or sequencing of targeted therapies for the treatment of mRCC. The findings are discussed from a clinical perspective with a focus on the future outlook of this disease.

2. Evidence acquisition

2.1. Search strategy

The methods protocol of the European Association of Urology (EAU) renal cell carcinoma 2013 guidelines was used as a basis for the search strategy. The guidelines incorporated a systematic review designed to compare the clinical effectiveness and safety of systemic treatments for mRCC including only RCTs or quasi-RCTs (eg, alternate allocation). Eligible trials must have included one of the prespecified systemic treatment agents, such as targeted therapy, vaccines, chemotherapy, or cytokines, in one of the trial arms. A valid comparator included any of the prespecified systemic therapy agents or placebo. For the present systematic review, the original EAU search was updated (covering the period from January 1, 2000, to September 30, 2013), and eligibility was restricted to RCTs related to combining or sequencing systemic targeted therapies only. The primary outcome of interest was PFS and OS; secondary outcomes were harms of treatment. The search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement [9].

The databases searched were Medline, Medline In-Process, Embase, Cochrane Controlled Trials Register (Cochrane Library, Issue 8, 2013), and the Latin American and Caribbean Center on Health Sciences Information System. The search was complemented by additional sources including systematic reviews from the Cochrane Database of Systematic Reviews (Cochrane Library, Issue 8, 2013), recent conference proceedings of the American Society of Clinical Oncology and European Society of Medical Oncology, ongoing trials from clinicaltrials.gov and the World Health Organisation International Clinical Trials Registry, reference lists of included studies that were hand-searched to identify additional relevant studies, and reports identified by the expert panel of coauthors.

2.2. Data collection and analysis

All abstracts and titles identified by the search were screened using a predefined study screening form. Two coauthors (F.H. and T.L.) independently performed abstract and full-text screening. Disagreement was resolved by discussion, and where no agreement could be reached, an arbiter (A.B.) was sought. In addition, studies included for qualitative analysis in the 2013 EAU guidelines were screened for inclusion in the present systematic review (ie, studies addressing sequencing or combining targeted therapies) by two coauthors (L.A. and A.B.). Some studies that did not meet the inclusion criteria for the evidence synthesis were retained for the background and discussion sections. A data extraction form was developed a priori specifically to collect information on study design, characteristics of participants, characteristics of interventions, and outcome measures. Data relating to the prespecified outcomes were extracted.

Risk of bias (RoB) assessment was performed using the standard Cochrane Collaboration RoB tool for RCTs. For data analysis, descriptive statistics were used to summarise baseline characteristics data. Quantitative synthesis (meta-analysis) was only performed for studies where there was no appreciable clinical or methodological heterogeneity. Both fixed effects and random effects models were used to derive the appropriate test statistic. For time-to-event data, hazard ratios (HRs) and 95% confidence intervals (CIs) obtained directly from studies or indirectly from presented Kaplan-Meier survival curves were used to compare results. In analysing dichotomous outcomes, relative risk with 95% CIs was used. Statistical heterogeneity between studies was assessed by visual inspection of plots of the data, the chi-square test for heterogeneity, and the I^2 statistic. Analysis was performed using Cochrane RevMan v.5.2 software. Where meta-analysis was not feasible, a qualitative synthesis was provided.