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Review – Kidney Cancer

A Systematic Review and Meta-analysis Comparing the Effectiveness and Adverse Effects of Different Systemic Treatments for Non-clear Cell Renal Cell Carcinoma

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Abstract

Context: While vascular endothelial growth factor-targeted therapy and mammalian target of rapamycin inhibition are effective strategies in treating clear cell renal cell carcinoma (ccRCC), the most effective therapeutic approach for patients with non-clear cell RCC (non-ccRCC) is unknown.
Objective: To systematically review relevant literature comparing the oncological outcomes and adverse events of different systemic therapies for patients with metastatic non-ccRCC.
Evidence acquisition: Relevant databases including MEDLINE, Embase, and the Cochrane Library were searched up to March 24, 2016. Only comparative studies were included. Risk of bias and confounding assessments were performed. A meta-analysis was planned for and only performed if methodologically appropriate; otherwise, a narrative synthesis was undertaken.
Evidence synthesis: The literature search identified 812 potential titles and abstracts. Five randomized controlled trials, recruiting a total of 365 patients, were included. Three studies compared sunitinib against everolimus, one of which reported the results for non-ccRCC as a subgroup rather than as an entire randomized cohort. Individually, the studies showed a trend towards favoring sunitinib in terms of overall survival and progression-free survival (PFS; Everolimus versus Sunitinib in Patients with Metastatic Non-clear Cell Renal Cell Carcinoma hazard ratio [HR]: 1.41, 80% confidence interval [CI]

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1.03–1.92 and 1.41, 95% CI: 0.88–2.27, Evaluation in Metastatic Non-clear Cell Renal Cell Carcinoma HR: 1.16, 95% CI: 0.67–2.01, Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients with Metastatic Renal Cell Carcinoma HR: 1.5, 95% CI: 0.9–2.8), but this trend did not reach statistical significance in any study. Meta-analysis was performed on two studies which solely recruited patients with non-ccRCC reporting on PFS, the results of which were inconclusive (HR: 1.30, 95% CI: 0.91–1.86). Sunitinib was associated with more Grade 3–4 adverse events than everolimus, although this was not statistically significant.

Conclusions: This systematic review and meta-analysis represent a robust summary of the evidence base for systemic treatment of metastatic non-ccRCC. The results show a trend towards favoring vascular endothelial growth factor-targeted therapy for PFS and overall survival compared with mammalian target of rapamycin inhibitors, although statistical significance was not reached. The relative benefits and harms of these treatments remain uncertain. Further research, either in the form of an individual patient data meta-analysis involving all relevant trials, or a randomized controlled trial with sufficient power to detect potential differences between treatments, is needed.

Patient summary: We examined the literature to determine the most effective treatments for advanced kidney cancer patients whose tumors are not of the clear cell subtype. The results suggest that a drug called sunitinib might be more effective than everolimus, but the statistics supporting this statement are not yet entirely reliable. Further research is required to clarify this unmet medical need.

1. Introduction

Renal cell carcinoma (RCC) accounts for approximately 2–3% of all malignancies with variations in regional incidence ranging from 10–31.4/100 person/yr in men [1]. While 15–17% of patients diagnosed with RCC are estimated to present with metastatic disease; in current nationwide cancer statistics, validated risk scores suggest that approximately 30% of nonmetastatic patients who underwent a nephrectomy will be diagnosed with metastasis within 5 yr of follow-up. For 2016, 62 700 new cases of kidney cancer are expected to occur in North America, although this figure does include cancer of the renal pelvis [2]. The predominant subtype is clear cell RCC (ccRCC; 80–90%) with all other subtypes collectively summarized as non-clear cell renal cancer (non-ccRCC). Among other rare subtypes 10–15% of all RCC account for the papillary and 4–5% for the chromophobe subtype. The burden of either synchronous or metachronous metastatic RCC is high, with approximately 38 000 patients being diagnosed annually in Europe based on the figures from 2012, among whom almost 8000 had non-ccRCC [3]. In contrast to ccRCC, metastatic non-ccRCC is less responsive to vascular endothelial growth factor (VEGF)-targeted therapy or inhibitors of the mammalian target of rapamycin (mTOR). A recent systematic review compared the non-ccRCC subpopulation from pivotal randomized controlled trials (RCTs) with the predominant clear-cell population included in the same trials [4]. However, amongst patients with non-ccRCC, the relative benefits and detriments of each drug remain unclear. Meanwhile, two RCTs recruiting only non-ccRCC patients comparing VEGF-targeted therapy against mTOR inhibitors (Evaluation in Metastatic Non-clear Cell Renal Cell Carcinoma [ESPN] and Everolimus versus Sunitinib in Patients with Metastatic Non-clear Cell Renal Cell Carcinoma [ASPEN]) [5,6] and one RCT recruiting non-ccRCC and ccRCC patients comparing the same drugs but reporting the results for each subgroup separately (Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients with Metastatic Renal Cell Carcinoma [RECORD3]) [7] have reported their findings. The present systematic review was aimed at determining the effectiveness and harms of systemic therapy for non-ccRCC to determine the current evidence base and identify knowledge gaps.

2. Evidence acquisition

2.1. Search strategy

The review was undertaken by the European Association of Urology (EAU) RCC Guidelines Panel, which is a multidisciplinary panel consisting of expert urological surgeons, oncologists, pathologists, radiologists, and patient representation, as part of its guidelines update for 2016. The review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [8]. The search was conducted in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions [9]. Studies were identified by searching electronic databases and relevant websites. Highly sensitive electronic searches were conducted to identify published and ongoing comparative studies of systemic treatment of non-ccRCC. Searches were limited to studies published from 2000 onwards but no language restrictions were imposed. The search was complemented by additional sources, including relevant systematic reviews and the reference lists of included studies which were hand searched to identify additional potentially relevant studies. Additional reports were identified by a reference panel (EAU RCC Guidelines Panel).

The databases searched were MEDLINE (1946 to May 2016), MEDLINE In-process (March 24, 2016), Embase (1974 to March 24, 2016), Cochrane Controlled Trials

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