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Immunotherapy versus standard of care in metastatic renal cell carcinoma. A systematic review and meta-analysis

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ABSTRACT

Background: Recently, immune checkpoint inhibitors against PD-1/PD-L1 or CTLA4 have emerged as new treatments for metastatic renal cell carcinoma (mRCC), despite discrepancy between their effects on OS and PFS. We performed a meta-analysis of randomized trials comparing immunotherapy to standard of care (SOC) in mRCC.

Methods: Searching the MEDLINE/PubMed, Cochrane Library and ASCO Meeting abstracts prospective studies were identified. Data extraction was conducted according to the PRISMA statement. The measured outcomes were OS, PFS, and ORR.

Results: A total of 2832 patients were available for evaluation of OS, and 3033 for PFS and ORR. Compared to SOC, immunotherapy improved OS (HR = 0.75; 95%CI 0.66–0.85; p < 0.001), and PFS (HR = 0.88; 95%CI 0.80–0.97; p = 0.009). The PFS benefit was not confirmed when considering patients treated in first-line only (p = 0.10). Conversely, significant ORR improvement was found in patients treated in first-line only (HR = 1.14; 95%CI 1.02–1.28; p = 0.03) but not in the overall population.

Conclusions: Immunotherapy improved OS compared to SOC in mRCC, irrespective of treatment line. In first-line, immunotherapy also increased the ORR compared to sunitinib. A lack of correlation between OS and PFS was confirmed, the latter to be used cautiously for the design and interpretation of trials involving immunotherapy in mRCC.

Introduction

Renal cell carcinoma (RCC) is the sixth most common diagnosis of cancer in men and the eighth in women in United States with an estimated 63,990 new cases and 14,400 deaths occurred in the 2017 [1]. In Europe, the incidence and the mortality of RCC are estimated to be 71,739 and 31,293 cases per years, respectively [2,3].

Genetic alterations in the von Hippel–Lindau tumor-suppressor gene (*VHL*) have been found to be responsible for the majority of the cases of sporadic clear-cell RCC. In the presence of these alterations, a hypoxia-like response occurs also in conditions of normoxia, leading to the accumulation of hypoxia inducible factors, transcription of hypoxia-inducible genes, and overproduction of a series of cytokines and growth factors involved primarily in angiogenesis (e.g., vascular endothelial growth factor [VEGF]), but also in cell growth, glucose uptake, and acid–base balance. VEGF and its receptors (VEGFRs), which are highly expressed on endothelial cells [4], have been found as attractive targets for molecular therapies, ultimately leading to the introduction in our therapeutic armamentarium of VEGFRs-Tyrosine Kinases Inhibitors (TKIs), (e.g. sorafenib, sunitinib, pazopanib, axitinib, tivozanib, lenvatinib and cabozantinib), as well as of the monoclonal antibody bevacizumab, directed against the circulating VEGF [5]. As a whole, agents targeting the VEGF/VEGFRs pathway have lead to a significant improvement in the progression free survival (PFS) of metastatic RCC patients, overall yielding a 13% decrease of the risk of death or progression when compared to interferon-alpha [6].

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On the other hand, the immune check point inhibitors targeting the negative regulators of the antitumor immune response, either PD-1/PD-L1 or CTLA4, recently emerged as novel active agents for the treatment of mRCC, although their benefit in terms of overall survival (OS) and overall response rate (ORR) is often paired with a lack of benefit in terms of PFS [5]. Moreover, recent evidences speculate about the predictive role of PD-L1 expression on primary tumor, but definitive conclusions still lack.

Considering the emerging role of the immunotherapy in mRCC, we aim to perform a systematic review and meta-analysis of the randomized trials comparing immune checkpoint inhibitors over anti-VEGF/VEGFRs agents in order to better define the role of this novel strategy for treatment of mRCC, as well as the predictive role of PD-L1 expression in patients receiving immunotherapy.

Patients and methods

Definition of outcomes

For each trial, independent of treatment line (i.e. first- or second-line) therapy with anti-PD-1/PD-L1 immune checkpoint inhibitor was considered as the experimental therapy, while sunitinib or everolimus as the control one. The OS and the PFS were evaluated in the experimental over the control arm based on the hazard ratios (HR) and relative 95% confidence intervals (CIs), while the overall response rate (ORR) was evaluated in the experimental over the control arm based on the risk ratio (RR) and relative 95% confidence intervals (CIs) set out in selected studies.

Selection of studies

We reviewed MEDLINE/PubMed, Cochrane Library and the abstracts presented at the American Society of Clinical Oncology (ASCO) conferences for citations until April 2018. The entry terms for the search were “renal cell carcinoma”, “nivolumab”, “atezolizumab”, “pembrolizumab”, “durvalumab”, “avelumab”. Articles presented at ASCO conferences were searched for in the meeting library of the ASCO university website (http://meetinglibrary.asco.org/) using the same criteria reported above. For MEDLINE/PubMed the search was limited to phase III or phase II clinical trials.

The following inclusion criteria have been adopted: randomized trials/studies reporting data in mRCC patients. Principal exclusion criteria were overlapping publications, lack of relevant outcome data, placebo-controlled studies, trials with non-standard control arm; similarly, preliminary data not yet reported in extensor were not included.

The summaries for the product characteristics were searched for at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. If more than one publication was found for the same trial, the most recent, complete and updated version was included in the final analysis.

Study quality was assessed using the Jadad 5-item scale, which takes into account randomization, double blinding and withdrawals. The final score ranged from 0 to 5 [7].

Data extraction

The data extraction was conducted independently by two co-authors (R.I. and C.C.) according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [8]. Any discrepancy was resolved by consensus between these two authors. The data extracted for each trial were: first author’s name, year of publication, trial phase, number of evaluable patients, number of treatment arms, type of treatment used in the experimental and the control arms, and the HRs for PFS and OS with the relative 95% CI and the number of patients who achieved tumor response for each arm. The analysis was

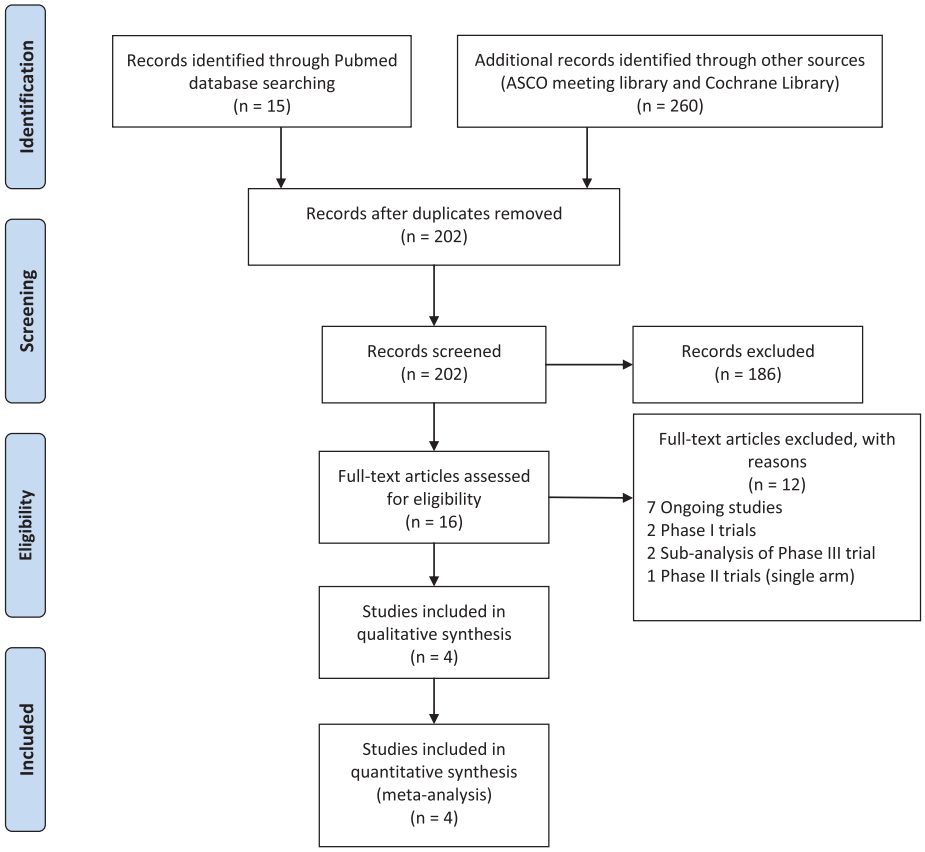

Fig. 1. Selection process for randomized controlled trials included in the meta-analysis.