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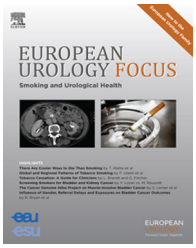

Review – Kidney Cancer

Immunotherapy for Renal Cancer: Sequencing and Combinations

Grant D. Stewart [a], *Maria De Santis* [b], *Bernard Escudier* [c], *Thomas Powles* [d], *Guru Sonpavde* [e,*]

[a] *Academic Urology Group, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK;* [b] *Cancer Research Centre, University of Warwick, Coventry, UK;* [c] *Gustave Roussy, Villejuif, France;* [d] *Bart's Cancer Institute, London, UK;* [e] *Department of Medicine, Section of Hematology-Oncology, University of Alabama at Birmingham (UAB), Birmingham, AL, USA*

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Abstract

Context: Current therapy for renal cell carcinoma (RCC) generally consists of the sequential administration of single agent therapy. Given the advent of T-cell checkpoint inhibitors, the role of combinations including these agents is being intensely interrogated.
Objective: To evaluate ongoing trials of combinations including immunotherapy and sequencing of agents to treat RCC.
Evidence acquisition: Recent data and ongoing trials were analyzed to evaluate the direction of research in this arena.
Evidence synthesis: The favorable therapeutic index of programmed cell death 1/programmed death-ligand 1 inhibitors enable combinations of these agents. Multiple ongoing phase 3 trials are evaluating the first-line therapy of RCC using a combination of programmed cell death 1/programmed death-ligand 1 inhibitors with vascular endothelial growth factor inhibitors or cytotoxic T-lymphocyte-associated protein 4 inhibitors. The role of sequencing using single agent sunitinib and avelumab will be evaluated in a randomized phase 2 trial. The role of vaccine therapy remains unproven. The role of predictive biomarkers to select appropriate therapy requires a greater focus, given the multitude of possible therapies.
Conclusions: Therapy for RCC should be tailored based on both patient and tumor characteristics. Combination therapy and sequencing of single agents may both play roles and are currently undergoing clinical trial evaluation.
Patient summary: Combinations of immunotherapy with angiogenesis inhibitors are undergoing vigorous clinical trial evaluations. Sequencing of immunotherapy and anti-angiogenic therapy is also undergoing investigation. Clinical trial participation is critically important to develop new drugs and combinations, and biomarkers to select therapy.

* Corresponding author. University of Alabama at Birmingham, Comprehensive Cancer Center, 1720 2nd Avenue South, Birmingham NP2540B, AL 35294, USA. Tel. +1-205-975-2914; Fax: +1-205-975-3910.
E-mail address: gsonpavde@uabmc.edu (G. Sonpavde).

1. Introduction

Renal cell carcinoma (RCC) is exquisitely resistant to chemotherapy. The chemoresistance may be partly attributable to the disease being derived from proximal tubules, which express large amounts of the multidrug resistant P-glycoprotein. Equally, relative to other malignancies, RCC has been particularly sensitive to immunotherapy. The first

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indication that RCC might be a good target for immunotherapy came from the observation that patients with metastatic RCC occasionally experienced spontaneous regressions after surgical removal of the primary tumor [1–3]. It is also well established that there is profuse inflammatory infiltrate in RCC, although the precise role of each infiltrating cell type (T-cells, natural killer cells, dendritic cells, and macrophages) is not established [4]. Until 2005, the median survival of patients with metastatic RCC (mRCC) was approximately 1 yr and the only treatments available were interleukin (IL)-2 and interferon (IFN)-α which conferred modest benefits [5]. A major step-forward started in 2005, when new targeted drugs including mammalian target or rapamycin (mTOR) inhibitors (everolimus, temsirolimus), vascular endothelial growth factor (VEGF) inhibitors (sunitinib, sorafenib, axitinib, pazopanib, cabozantinib), and a programmed death (PD)-1 inhibitor (nivolumab) were approved [6,7]. Additionally, the combination of a VEGF inhibitor plus cytokine (bevacizumab plus IFN-α) and VEGF inhibitor plus mTOR inhibitor (lenvatinib plus everolimus) have demonstrated improved outcomes in the first-line and post-VEGF inhibitor settings, respectively, and are approved. Thus, the treatment algorithm includes the use of sunitinib, pazopanib, bevacizumab plus IFN-α or temsirolimus as first-line therapy, and nivolumab, cabozantinib, axitinib or lenvatinib plus everolimus as second-line therapy. Collectively, these agents have extended the median survival of mRCC patients to 2–2.5 yr. High dose IL-2 is reserved as first-line therapy for well selected younger patients without comorbidities.

Since 2015, there has been a further paradigm shift in the management of mRCC with the addition of nivolumab, a T-cell checkpoint inhibitor, to the therapeutic armamentarium for post-VEGF inhibitor patients. The next generation of immunotherapeutics has been established to be of benefit in mRCC. Harnessing the immune system has long been of interest because of the potential for durable responses, initially seen with cytokine treatment [8]. The step change in the mechanism of action that T-cell checkpoint inhibitors provide is that of immunoediting, that is, altering the balance between the tumor and the immune system [9]. In the elimination phase CD8+ T-cells and natural killer cells destroy a proportion of malignant cells, the surviving cancer cells survive in a constrained state in the presence of immune cells in the equilibrium phase, before entering the escape phase where cancer cells evade immune cell recognition [9]. T-cell checkpoint inhibitors such as PD-1 inhibitors can alter this balance by unleashing the antitumor activity of T-cells in the tumor microenvironment [10].

It remains the case that most patients will not show a major durable response to single-line immune therapy [11]. As such, combination and sequential therapies are being evaluated. Vanneman and Dranoff [12] have described different potential mechanisms by which combination therapy strategies may work: (1) enhance antigen presentation and T-cell priming, (2) augment differentiation of memory T cells, (3) improve antitumor T-cell function, (4) enhance cytotoxic T lymphocyte (CTL)-mediated lysis of tumor cells, (5) reduce tumor-associated immunosuppression, and (6) decrease immunosuppressive cell populations.

In view of the increasing number of drugs with differing mechanisms of action in the arsenal of the oncologist, the next questions being answered by clinical trials are the role of sequential or combinatorial therapy with immunotherapeutic agents. Ongoing trials are evaluating the combination of PD-1/PD-ligand (L)-1 inhibitors with either VEGF inhibitors or CTL antigen (CTLA)-4 inhibitors as first-line therapy (Table 1). In this review, we will summarize this literature and plot a future course.

2. Evidence acquisition

2.1. Search criteria

A literature search was performed using PubMed (January 1976 to March 2017).

2.2. The past: cytokines and historically evaluated combinations

IFN-α and high-dose (HD) IL-2 are the two cytokine therapies which have been proven to be efficacious in mRCC treatment [13]. The exact mechanism by which these agents work is unclear. However, IL-2 is known to stimulate T-cell proliferation and differentiation and IFN-α is antiangiogenic as well as a promoter of antigen presentation and dendritic cell development [4]. IL-2 is a toxic regimen, requiring inpatient administration and resulting in up to 3% patients dying from treatment; however, there is a 7% complete response (CR) rate, most of them being durable and potential cures, and around 15% patients have an

Table 1 – Ongoing randomized phase 3 combination T-cell checkpoint inhibitor trials in metastatic clear cell renal cell carcinoma.

Therapeutic target	Line	Control arm	Experimental arm(s)
PD-1 and CTLA-4	First	Sunitinib	Nivolumab + ipilimumab × 4 → Nivolumab
PD-1 and VEGF	First	Sunitinib	Bevacizumab + atezolizumab
PD-L1 and VEGF	First	Sunitinib	Axitinib + avelumab
PD-L1 and VEGF	First	Sunitinib	Axitinib + pembrolizumab
VEGF/FGF and (PD-1 or mTOR)	First	Sunitinib	Lenvatinib + pembrolizumab OR Lenvatinib + everolimus
Vaccine (dendritic cell-based vaccine + autologous tumor cell mRNA + CD40 ligand)	First	Sunitinib	Sunitinib + AGS-003

CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; FGF = fibroblast growth factors; mRNA = messenger RNA; mTOR = mechanistic target of rapamycin; OR = overall response; PD-1 = programmed death 1; PD-L1 = programmed death-ligand 1; VEGF = vascular endothelial growth factor.