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Review article

Second-line systemic therapy in metastatic renal-cell carcinoma: A review

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Abstract

Treatment in metastatic renal-cell carcinoma (mRCC) has evolved tremendously in the last decade. The development of newer targeted agents, like vascular endothelial growth factor inhibitors and immunotherapy have changed the treatment paradigm in mRCC patients. Axitinib and everolimus have been used extensively in patients who progressed on prior antiangiogenic therapy. The newer agents including nivolumab, cabozantinib, and lenvatinib in combination with everolimus have all demonstrated overall survival benefit over everolimus. However, with multiple treatment options, optimal choice and sequencing becomes challenging. This article provides an overview of different therapeutic options available as second-line treatment in patients with mRCC along with future directions.

Keywords: Metastatic renal-cell carcinoma; Second-line; Immunotherapy

1. Introduction

Kidney cancer is the eighth most common cancer with estimated 63,990 new cases and 14,400 deaths in 2017 [1]. Its incidence is rising at an average of 1.1% each year with 16% of the cases being metastatic at the time of presentation [2]. With better detection techniques and novel treatment options, the 5-year survival for advanced kidney cancer has increased from 7.3% (during 1992–1995) to 11.6% (during 2006–2012) [2]. Approximately 90% of kidney tumors are renal-cell carcinoma (RCC), 80% of which is composed of clear-cell histology. Other less common cell types include papillary, chromophobe, and collecting duct tumors.

Von Hippel Lindau (*VHL*) gene mutations on chromosome 3 play a key role in the development and pathogenesis of both inherited and sporadic clear-cell RCC [3]. *VHL* is a tumor suppressor gene and its protein product pVHL is a regulator of hypoxia inducible factors [4]. *VHL* inactivation leads to hypoxia inducible factor up-regulation causing increase in angiogenic peptides like vascular endothelial growth factor (VEGF) [5]. PI3K/AKT/mTOR pathway, which control cell metabolism, growth, and survival, has also been extensively studied in RCC. These molecular findings led to the emergence of therapies like VEGF receptor tyrosine kinase inhibitors (TKIs), anti-VEGF monoclonal antibody bevacizumab, mTOR inhibitors and immune checkpoint inhibitor (CPIs), nivolumab which have demonstrated remarkable effects on patient outcomes. The first-line options for metastatic RCC (mRCC) include sunitinib, pazopanib, bevacizumab + interferon alpha (IFNα), temsirolimus (in poor risk/nonclear-cell histology) and high dose interleukin-2 (HD-IL-2) in very selective patients. This review will focus on current clinical data and future directions for second-line treatment strategies (Table 1) in mRCC patients.

2. Methods

We queried PubMed for all published clinical trials of the currently Food and Drug Administration (FDA) approved drugs in second-line treatment setting for mRCC. These articles were than included for the purpose of this review. This is not a systematic review and therefore we have not used a checklist like PRISMA for inclusion of articles.

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Table 1
List of established systemic agents in second-line treatment for mccRCC patients

Trial	Standard (S)	Comparator (C)	PFS (S vs. C) in mo	OS (S vs. C) in mo	ORR	S related grade 3 or 4 toxicity
AXIS [24]	Axitinib	Sorafenib	6.7 vs. 4.7 ($P < 0.001$)[a]	20.1 vs. 19.2 ($P = 0.37$)[b]	19% vs. 9%	Hypertension, diarrhea, fatigue
METEOR [19]	Cabozantinib	Everolimus	7.4 vs. 3.8 ($P < 0.001$)[a]	21.4 vs. 16.5 ($P = 0.003$)[a]	21% vs. 5%	Hypertension, diarrhea, fatigue
Motzer et al. [21]	Lenvatinib + everolimus	Everolimus	14.6 vs. 5.5 ($P = 0.003$)[a]	25.5 vs. 15.4 ($P = 0.02$)[a]	43% vs. 6%	Diarrhea, hypertension, fatigue
CheckMate 025 [14]	Nivolumab	Everolimus	4.6 vs. 4.4 ($P = 0.11$)[b]	25 vs. 19.6 ($P = 0.002$)[a]	25% vs. 5%	Fatigue, nausea, diarrhea
TARGET [27]	Sorafenib	Placebo	5.5 vs. 2.8 ($P < 0.01$)[a]	17.8 vs. 15.2 ($P = 0.15$)[b]	2% vs. 0%	Diarrhea, rash, hand-foot syndrome
RECORD-1 [30]	Everolimus	Placebo	4.9 vs. 1.9 ($P < 0.001$)[a]	14.8 vs. 14.4 ($P = 0.16$)[b]	1.5% vs. 0%	Stomatitis, infections, pneumonitis

[a]Statistically significant.
[b]Not statistically significant.

3. Immune CPIs

RCC is considered to be an immunogenic tumor and before the approval of immune CPIs, HD-IL-2 and IFN-α were the only available approved immunotherapy treatment options for mRCC patients [6]. However, only 10% to 20% of patients responded to these treatments and were also not very well tolerated. CPIs block immune inhibitory signals and restore a patient's natural tumor specific T-cell-mediated immune response. Programmed death-1 (PD-1) and its ligand (PD-L1) have been identified as novel therapeutic targets for CPIs and are predominantly expressed on several antigen-presenting cells or activated T-cells. Of the 2 PD-1 ligands, PD-L1 protein is expressed on antigen-presenting cells, activated T-cells, and other immune cells [7,8] whereas PD-L2 expression is limited to macrophages, dendritic cells, and B-cells [8,9]. Binding of PD-L1 to PD-1 negatively regulates immune system, inhibiting intracellular PI-3 kinase activity, cytokine release, downstream AKT activation, and other stimulatory pathways within the T-cells. Hence, the PD-1/PD-L1 and PD-L2 interaction results in the tumor generating resistance to the endogenous immune responses aiding tumor proliferation [8,10].

Nivolumab, a fully human immunoglobulin (Ig) G4 (PD-1) CPI enhances the innate immune system by blocking PD-1 and targeting the coinhibitory molecules, PD-L1 and PD-L2 [11,12]. It has demonstrated safety, efficacy, and superiority to standard of care in the second-line treatment of mRCC [13,14].

3.1. Phase II data

An international, multicenter, phase II trial of nivolumab was conducted in treatment-refractory mRCC patients based on the favorable toxicity profile and promising efficacy in phase I trial [12]. A total of 168 metastatic clear-cell RCC (mccRCC) patients with at least one prior VEGF-TKI therapy were randomized to receive nivolumab 0.3, 2, or 10 mg/kg once every 3 weeks until disease progression or intolerance to treatment [13]. The primary endpoint was progression-free survival (PFS) across the different dose groups to analyze any dose-response relationships. Secondary endpoints included overall response rate (ORR), overall survival (OS), time to response, duration of response and safety. A total of 70% of patients had received more than 1 prior VEGF-TKI therapy. After a minimum follow-up of 38 months, the median PFS (mPFS) (2.7, 4, and 4.2 mo) and OS (18.5, 25.5, and 24.8) did not differ significantly across the dose cohorts of 0.3, 2, and 10 mg/kg. ORR was also similar across the 3 groups (20%–22%). Among objective responders, ongoing responses of 75%, 50%, and 45% were seen even after cessation of treatment in the dose cohorts of 0.3, 2, and 10 mg/kg, respectively. PD-L1 expression with cutoff of 5% was measured in the archival tissue in an effort to establish a predictive biomarker. PFS, OS, and response rate were higher