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EDITORIAL

Immunotherapy in renal cell carcinoma: latest evidence and clinical implications

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Abstract

Advances in understanding the mechanisms of tumour-induced immunosuppression have led to the development of immune-checkpoint inhibitors in cancer patients, including those with renal cell carcinoma (RCC). The optimal combination between immunotherapy and targeted agents (as well as the possible favourable sequential therapy of these two classes of drugs) remains an open question at this moment. Several trials are currently underway to assess the combination of anti-programmed-death 1 (PD-1) or anti-PD-ligand(L)1 agents with other immunotherapies or with anti-vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs). In this editorial, we described the results of the most recent clinical trials on the use of immunotherapies in RCC and the emerging data on the research for reliable biomarkers of tumour response in this setting. In addition, we have focused on the role of the gut microbiome and tumour microenvironment in the development of future therapeutic strategies for RCC patients.

Keywords: immunocheckpoint inhibitors, immunotherapy, PD-1, renal cell carcinoma, tyrosine kinase inhibitors.

Citation

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Introduction

Less than ten years ago, there were only a few drugs with demonstrated clinical efficacy in the management of metastatic renal cell carcinoma (mRCC) but without significant impact on clinical outcomes. However, in recent years, the approval of several agents has revolutionized treatment. Indeed, every new drug approved has provided a further step in the improvement of patient survival. Consequently, it is important to have a better understanding of tumour biological features as well as genetic assessment. Thus, we have discovered that renal cell carcinoma (RCC) involves a very large spectrum of tumours. Each of them is composed of a different spectrum of mutations and with different clinical behaviour. Clear cell RCC (ccRCC) accounts for approximately 75% of kidney cancer. In contrast, the other 25% of kidney cancer is classified as nonclear cell RCC (nccRCC). Of this last subgroup of tumours, the World Health Organization recognized a broad spectrum of over a dozen histopathological entities in 2016. Papillary renal cell carcinoma (pRCC) and chromophobe RCC (chRCC) are the most frequent subtypes of nccRCC; whereas, medullary, translocation and collecting duct RCC represent an infrequent diagnosis [1]. Each tumour subtype presents a specific and complex spectrum of gene and molecularly altered pathways resulting in a heterogeneous mixture of malignancies associated with different morphology, immunohistochemical features, clinical behaviour and prognosis.

Our growing understanding of the molecularly altered pathways related to cancer has led to the development of new classes of drugs that have rapidly replaced the first immunotherapies such as interleukin (IL)-2 and interferon-alfa (IFN-alfa) as the standard of care for RCC patients. Angiogenesis, the hallmark of RCC, is the first final target of several tyrosine kinase inhibitors (TKIs) (sunitinib, axitinib, sorafenib and pazopanib). After angiogenesis, the finding that deregulation of the PI3K–Akt–mTOR pathway, activated at different levels of the signalling cascade, drives RCC progression has led to the development of two mTOR inhibitors: everolimus and temsirolimus. Recently, the mesenchymal-epithelial transition

(MET) and multityrosine kinases inhibitor cabozantinib has been included in clinical practice.

These drugs have led to an improvement in overall survival (OS) (sunitinib, pazopanib and cabozantinib) and in progression-free survival (PFS) (sunitinib, axitinib, cabozantinib, sorafenib, pazopanib, everolimus and temsirolimus), which was the endpoint of interest for FDA approval, until recently. All of these drugs showed a good safety profile combined with remarkable clinical activity in a disease that has always been difficult to treat [2–10].

Immune-checkpoint inhibitors

Although these drugs have significantly changed the course of this disease, the latest class of agents, the immune-checkpoint inhibitors, are predicted to provide further benefit. Programmed death receptor 1/programmed death receptor ligand 1 (PD-1/PD-L1) and cytotoxic T lymphocytes antigen 4 (CTLA-4) inhibitors target specific pathways related to the immune response, which are often hyperactivated by tumour cell interaction. By inhibiting these pathways, immune-checkpoint inhibitors could reactivate a specific immune response against tumour cells. The observation that RCC is related to a high mutation load and so maybe to high antigen expression has led to these drugs being tested at different stages of the disease. CheckMate 025 was the first large phase III clinical trial comparing the PD-1 inhibitor, nivolumab, to everolimus in patients with locally advanced or metastatic RCC who had progressed to at least one VEGF/VEGFR inhibitor. This study met its primary endpoint showing an OS benefit in patients receiving nivolumab. Furthermore, patients treated with immunotherapy showed a higher overall response rate (ORR) compared to everolimus with a considerable percentage of these achieving long-lasting response [11]. It is not surprising that the important results achieved in this trial led researchers to explore immunotherapy in other settings such as adjuvant/neoadjuvant stage and as first-line therapy [12–14]. Of note, Motzer and colleagues recently reported results of CheckMate 214, a phase III trial that tested the combination of ipilimumab and nivolumab over sunitinib in previously untreated patients with intermediate/poor risk (according to IMDC) metastatic or locally advanced ccRCC. The combination resulted in a significant OS benefit (median overall survival not reached *versus* 26.0 months with sunitinib, hazard ratio [HR] 0.63) in this population of patients. In addition, ORR was significantly better in the combination arm (42% with 9% of CR) compared to sunitinib (27% with 1% of CR).

Regarding this last point, two different strategies have been adopted.

Combination of an immune-checkpoint inhibitor and a VEGF inhibitor

The combination of an immune-checkpoint inhibitor and a VEGF inhibitor has been evaluated in phase II trials. In the IMmotion150 study, 305 patients with locally advanced/mRCC and untreated RCC were randomized to receive atezolizumab (an anti-PD-L1 inhibitor) plus bevacizumab, atezolizumab alone or sunitinib. The combination arm resulted in a longer PFS compared to atezolizumab (6.1 months) and sunitinib arms with a higher percentage ORR in the combination arm. Of note, patients with PD-L1 positive expression (≥1%) showed a longer PFS (14.7 months) and higher ORR (46%) in the atezolizumab monotherapy arm [15].

The combination of two immune-checkpoint inhibitors has been recently tested in a large phase III trial: CheckMate 214. In this study, patients were randomized to receive nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA-4) or sunitinib as first-line therapy. At the 2017 ESMO Conference, Escudier presented primary results after 17.5 months of follow-up showing that the ipilimumab plus nivolumab combination resulted in higher ORR and CR in intermediate/poor-risk patients. Of note, patients with intermediate/poor-risk disease and PD-L1 expression ≥1% showed higher ORR and PFS compared to sunitinib; whereas, patients with favourable category of risk (which showed lower PD-L1 expression) showed a longer PFS and a higher ORR with sunitinib [16].

These encouraging results may only be the 'tip of the iceberg' and could suggest that we are entering a new era for the management of mRCC. Nonetheless, even if immunotherapy represents a new hope for patients with mRCC, the relatively older targeted therapy is far from being abandoned. In other words, although CheckMate 025 showed that nivolumab is better than everolimus, there are other agents that are extremely effective after VEGF/VEGFR inhibitors progression; thus, the decision for second-line treatment should be weighed on the basis of the clinical outcome pursued as well as patient preference and drug toxicity profile. Immunotherapy has shown very interesting result in first-line therapy. Looking to CheckMate 214 results, it is probable that this positive effect could be restricted in patients with specific clinical features such as intermediate/poor-risk disease; whereas, patients with a favourable profile could benefit more from a standard treatment [14]. This would suggest that the worst clinical profile of the disease could be related to a high mutation load of tumour cells resulting in a higher antigen expression. In addition, preliminary data seem to indicate that these patients present a higher percentage of tumours with positive PD-L1 expression. However, to date, no mature data about the role of immunotherapy in favourable risk patients have been released. Furthermore, in an exploratory analysis of CheckMate 214, immunotherapy also showed a not-to-be-ignored clinical activity in patients with favourable risk (CR 11 *versus* 6%) even if the same combination was associated with a worse ORR (29 *versus* 52%) compared to sunitinib. Future studies will help us to better understand the role of PD-L1 as a prognostic and predictive response factor because, to date, we have strongly diverging information. Indeed, a meta-analysis of six published studies revealed that a higher level of PD-L1 expression increased the risk of death by representing, therefore, a negative prognostic factor [17]. Different to what was expected,

Table 1. Results obtained in trials exploring immune-checkpoint inhibitors in metastatic/locally advanced RCC.

Study name Experimental arm Comparator arm	Setting	N ITT	N PD-L1+	OS ITT	HR	OS PD-L1+	PFS ITT	HR	PFS PD-L1+	HR	ORR ITT	ORR PD-L1+	CR
CHECKMATE 025													
Nivolumab	Previously treated patients with locally advanced or mRCC	410	94	25.0	0.73	21.8	4.6	0.88	NR	NR	25%	NR	1%
Everolimus		411	87	19.6		18.8	4.4		NR		5%	NR	<1%
IMMOTION150													
Atezolizumab + bevacizumab	Untreated patients with locally advanced or mRCC	101	164	NR	NR	NR	NR	NR	NR	NR	32%	46%	NR
Atezolizumab		103		NR		NR	NR		NR		25%	28%	NR
Sunitinib		101		NR		NR	NR		NR		29%	27%	NR
CHECKMATE 214													
Ipilimumab + nivolumab	Untreated patients with locally advanced or mRCC	550	204	NR	NR	NR	11.6	0.82	22.8*	0.48	NR	58%*	9.4%*
Sunitinib		546	224	NR	NR	NR	8.4		5.9*		NR	25%*	1.2%*

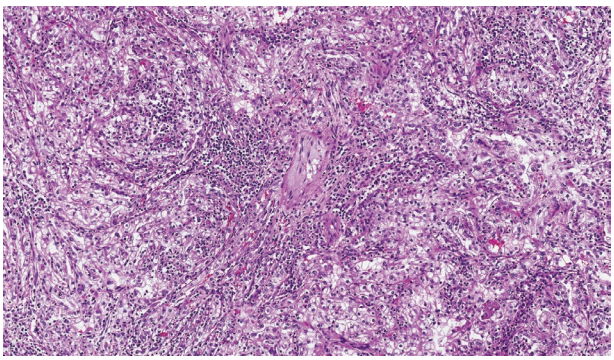
CR, complete response; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
*Intermediate/poor-risk patients with PD-L1 expression ≥1%.

the improved OS with nivolumab was not correlated with PD-L1 expression in CheckMate 025; whereas, patients with positive PD-L1 expression seemed to show more clinical benefit from immune-checkpoint inhibitors in IMmotion150 and CheckMate 214 (Table 1).

Future challenges

The complex interplay of inflammatory mediators and signalling pathways is absolutely crucial for RCC development and response to therapy [18–22] (Figure 1). Neutrophils, lymphocytes and macrophages have been implicated in promoting tumour angiogenesis and metastatic spread, as well as in the formation of pre-metastatic niches and in primary and acquired drug resistance [18–22]. In this scenario, the checkpoint molecules have gained wide interest since the introduction of anti-CTLA-4 and anti-PD-1/PD-L1 agents into daily clinical practice [23]. Beyond PD-1 and CTLA-4, a variety of molecules are emerging as potential therapeutic immunotargets in RCC [24]. This list includes the V-domain immunoglobulin containing suppressor of T-cell activation (VISTA), which has been recently shown to exert its inhibitory activity by acting as a ligand on antigen presenting cells (APCs) and as a receptor on T cells [25–27], chemokine receptors [28], the soluble lymphocyte-activation gene-3 (LAG-3), 4-1BB, B and T lymphocyte attenuator (BTLA) and OX40 (CD134) [29].

Figure 1. Clear cell renal cell carcinoma (ccRCC) with chronic inflammation.



At present, we do have full knowledge of the underlying mechanisms of immune-checkpoint inhibitors-induced tumour response. To address this issue, Wei and colleagues investigated the effects of anti-PD-1 and anti-CTLA-4 inhibitors in human melanoma and murine tumour models [30]. They first revealed that these agents are able to target distinct tumour-infiltrating T-cell subpopulations. In particular, PD-1 blockade promotes the expansion of specific exhausted-like CD8 T-cell populations; whereas, CTLA-4 blockade induces both an $ICOS^+$ Th1-like CD4 effector subset and exhausted-like CD8 T cells [30].

Table 2. Ongoing phase III clinical trials testing the association between immunotherapy and TKIs.

Trial	Treatment arms	n	Setting	Estimated primary completion date
NCT02811861	Sunitinib *versus* lenvatinib + everolimus *versus* lenvatinib + pembrolizumab	735	First line	October 2019
NCT02684006	Avelumab + axitinib *versus* sunitinib	830	First line	December 2018
NCT03141177	Nivolumab + cabozantinib *versus* sunitinib	630	First line	September 2019
NCT02420821	Atezolizumab + bevacizumab versus sunitinib	915	First line	July 2020
NCT02853331	Pembrolizumab + axitinib *versus* sunitinib	840	First line	January 2020

This evidence strongly supports the results of different trials exploring this combination therapy in different diseases and favours the combined use of current and future checkpoint inhibitors in cancer patients, which seems to be characterized by a good tolerable safety profile [14,31–33].

The results obtained in recent years have raised enormous enthusiasm in cancer researchers, aimed at identifying, isolating and validating biomarkers associated with the dynamics of the tumour environment and the therapeutic response [17,34,35]. Indeed, tumour responsiveness varies according to the mutation load and the expression of immunotargets in the tumour environment, which is variable in the different phases of RCC development and progression [36]. Based on this evidence, assessing the expression of PD-1/PD-L1 or other emerging immunotargets only at the diagnosis of metastatic disease may not reflect tumour dynamicity. To improve the feasibility and reduce the clinical impact of re-biopsy, assessing biomarkers on circulating tumour cells (CTCs) or exosomes [37] may represent a noninvasive strategy that can be performed several times during cancer therapy to reflect changes that occurred in the tumour environment. The early identification of validated biomarkers will be crucial to definitively carry immunotherapy into the era of precision medicine and to optimize the cost-effectiveness of these agents in cancer patients [38,39].

More recently, Routy and colleagues revealed that primary resistance to immune-checkpoint inhibitors can be correlated with abnormal gut microbiome composition [40]. In this study, the effectiveness of PD-1 blockade was enhanced by transplanting faecal microbiota from responder cancer patients into germ-free or antibiotic-treated mice [40], thus representing another step on the way to personalized and precision immunotherapy in cancer patients.

Another factor that is fundamental to improve the efficacy of immunotherapy in RCC patients is a better understanding of the immunological effects of TKIs and mTOR inhibitors [18,41]. Indeed, these agents can indirectly exert their anti-tumour activity by targeting immune cells in the RCC microenvironment [18], and this should be considered to combine or sequence them with currently available and future immunotherapies. In this regard, sunitinib has been shown to inhibit the colony forming units (CFUs) driven by GM-CSF and FLT3 ligand (FLT3L) [42] as well as dendritic cell antigen presentation [40] (by decreasing the secretion of cytokines and the expression of MHC and CD1a molecules), to suppress the myeloid-derived suppressor cells (MDSCs, involved in RCC progression and drug resistance), to enhance tumour cell sensitivity to natural killer (NK) cell killing [43] and to reduce the total count of CD3 and CD4 T cells and regulatory T cells [44,45]. On the other hand, pazopanib showed lower inhibitory potency and affinity against FLT3 and c-kit compared to sunitinib [46]. Interestingly, we previously showed that axitinib can increase the surface NKG2D ligand expression, thus promoting NK cell recognition and degranulation in A-498 RCC cells in a ROS-dependent manner [47]. At present, little evidence is available on the immunomodulatory effects of cabozantinib and lenvatinib, both of which were recently introduced into RCC clinical practice. With regard to the association between immunotherapy and TKIs, the association between atezolizumab and both bevacizumab [48] and cabozantinib [49] as well as pembrolizumab and axitinib [50] has shown promising results in terms of clinical activity and safety profile – thus justifying the planning of several different

large trials exploring these associations in metastatic/locally advanced RCC (Table 2).

Conclusions

Optimizing the combination of immunotherapy and target agents, as well as the possible favourable sequence of treatment between these two classes of drugs, remains as open questions at this moment. We have only few data provided from IMmotion150, which demonstrated that association between a PD-L1 inhibitor and bevacizumab is feasible with a satisfactory safety profile. However, we do not know if this association results in an effective clinical benefit from our patients. Finally, it is important to observe that all the cited studies explored immunotherapy in patients with ccRCC and the role of immunotherapy still remains unknown in nccRCC.

There are several questions that need to be answered. It is undeniable that immunotherapy represents a revolution for the management of RCC resulting in a dynamic and evolving scenario. Future studies will increase our knowledge about the role of immunotherapy in this no-more orphan disease.

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