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Review Articles

Checkpoint inhibition: the current treatment of renal cell carcinoma

Inhibición de puntos de control: el tratamiento actual del carcinoma de células renales

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Abstract

Immune surveillance is one of the most important hallmarks of cancer. In the last decade many advancements in cancer treatment have been developed, much of them are related to the use of the immune system. Renal Cell Carcinoma is the most frequent type of kidney cancer followed by urothelial carcinoma. For years, treatment of Renal Cell Carcinoma has been conflictive as these tumors do not respond well to chemotherapy and have shown to be susceptible to immunotherapies as interferon and interleukin 2. The discovery of the immune checkpoints and their possible roles in cancer treatment led to the synthesis of novel drugs that can target and inhibit the interaction of certain molecules that are important for immunologic homeostasis. In this concise review, we summarize the evidence related with immune checkpoint inhibition for the treatment of renal cell carcinoma, especially for metastatic renal cell carcinoma.

Keywords:
immunotherapy, renal cell carcinoma, immune checkpoint, overall survival

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Resumen

La vigilancia inmunológica es una de las características más importantes del cáncer. En la última década se han desarrollado muchos avances en el tratamiento del cáncer, muchos de ellos relacionados con el uso del sistema inmunológico. El carcinoma de células renales es el tipo de cáncer de riñón más frecuente seguido del carcinoma urotelial. Durante años, el tratamiento del Carcinoma de Células Renales ha sido conflictivo ya que estos tumores no responden bien a la quimioterapia y han demostrado ser susceptibles a inmunoterapias como el interferón y la interleucina 2. El descubrimiento de los puntos de control inmunitarios y su posible papel en el tratamiento del cáncer llevó a la síntesis de nuevos fármacos que pueden dirigirse e inhibir la interacción de ciertas moléculas que son importantes para la homeostasis inmunológica. En esta revisión concisa, resumimos la evidencia relacionada con la inhibición del punto de control inmunitario para el tratamiento del carcinoma de células renales, especialmente para el carcinoma metastásico de células renales.

Palabras clave: inmunoterapia, carcinoma de células renales, punto de control inmunitario, supervivencia global

Introduction

Cancer is a multifactorial process in which multiple genes get involved at different stages of the disease. Some key regulatory genes, when mutated are called driver mutations, these mutations induce proliferation and start a process of adaptation and immortality in tumor cells.[1] Multiple physiological mechanisms of cell division and growing control are altered in cancer, these are known as the hallmarks of cancer.[2] In the last decades, cancer systemic treatments have been migrating from chemotherapy to targeted therapy and immunotherapy.[3] Different metastatic tumors have been demonstrated to improve considerably after immunotherapy trials, this is true mainly for lung cancer and melanoma.[4–6]

Renal Cell Carcinoma (RCC) is the most common type of kidney cancer, followed by urothelial carcinomas of the renal pelvis. The current prognosis for patients presenting with stage IV disease is poor. Immunotherapy stands as an improved approach of first-line interventions that are improving overall survival (OS), progression-free survival (PFS) and quality of life in these patients.[7] In this comprehensive review, we analyzed the mechanisms of immune checkpoint inhibition and the evidence that proposes this intervention as an important tool against metastatic RCC.

The role of immune surveillance in renal cell carcinoma

One of the hallmarks of cancer pathogenesis is the evasion of the immune system.[2] The innate and adaptive immune systems play a key role in avoiding cancer development. During tumor development, different neo-antigens are formed by tumor cells which are then processed and presented by professional antigen-presenting cells to T cells,[8] inducing an immune adaptive cellular response mediated by CD4+ and CD8+ T cells against tumor cells.[9]

Cancer behaves as an evolutionary microenvironment in which tumor cells try to adapt to challenges that face them.[10] Positive selection of mutant clones will allow tumor cells to evade immune surveillance by different means. One of the most important mechanisms by which cancer cells escape immune surveillance are called the immune checkpoints. A variety of immune checkpoints evolved as a strategy to decrease and even stop immune system effector mechanisms when an adequate immune response was achieved.[11] This mechanism is thought to be one of the key regulators of self-antigen tolerance, as continuous activation of the immune system could lead to autoimmune disorders. Two immune checkpoints have revolutionized cancer treatment in the last decade, the PD-1/PD-L1 and the CTL4-B7. These immune checkpoints when activated induce immune cells, specifically T-cells into anergy and even apoptosis.

RCC, accounts for approximately 3% of cancer cases worldwide and corresponds to 80-85% of all kidney cancer cases.[12–14] Approximately 30% of patients present with metastatic disease at diagnosis (mRCC) and under 20-40% of patients with localized disease will develop metastasis.[15] 5-year overall survival (5y-OS) for patients with metastatic disease is <10%.[16,17] Seventy percent of RCC correspond to clear cell histology (ccRCC).[18] Therefore, most evidence for systemic therapy in mRCC has been proven on this particular subtype.[19]

Current therapy for mRCC is categorized according to risk stratification and include agents like multi-targeted tyrosine kinase inhibitors (TKI) (pazopanib, cabozantinib, etc), cytokine therapy with interleukin-2 (IL-2) and interferon (IFN), immunotherapy with anti-angiogenic agents like bevacizumab and lately, and reserved to the worst prognosis risk-stratified patients, immunotherapy with immune checkpoint inhibitors (nivolumab and ipilimumab) as well as mTOR inhibitors like everolimus and temsirolimus.[19]

RCC is usually a tumor resistant to chemotherapy. It is well-known that RCC is a highly immunoresponsive tumor in which immune surveillance is usually addressed in order to induce anti-tumor responses.[20,21] Different immunomodulatory therapies have been approved for the treatment of RCC as they can achieve complete and durable remissions in a subset of patients with metastatic disease.[22,23]

Regarding immune checkpoints, different experimental studies have demonstrated that PD-L1 is expressed in tumor cells as well as in tumor infiltrating lymphocytes (TILs) in patients with RCC Thompson *et al.,* found that PD-L1 is expressed in about 66% of ccRCC cases.[24] Furthermore, patients presenting with a high PD-L1 expression had advanced stages, rapid metastatic progression and an overall worse prognosis.[19,21,24] Jilaveanu *et al.,* demonstrated that PD-L1 expression is significantly higher in metastatic lesions than in nephrectomy-derived

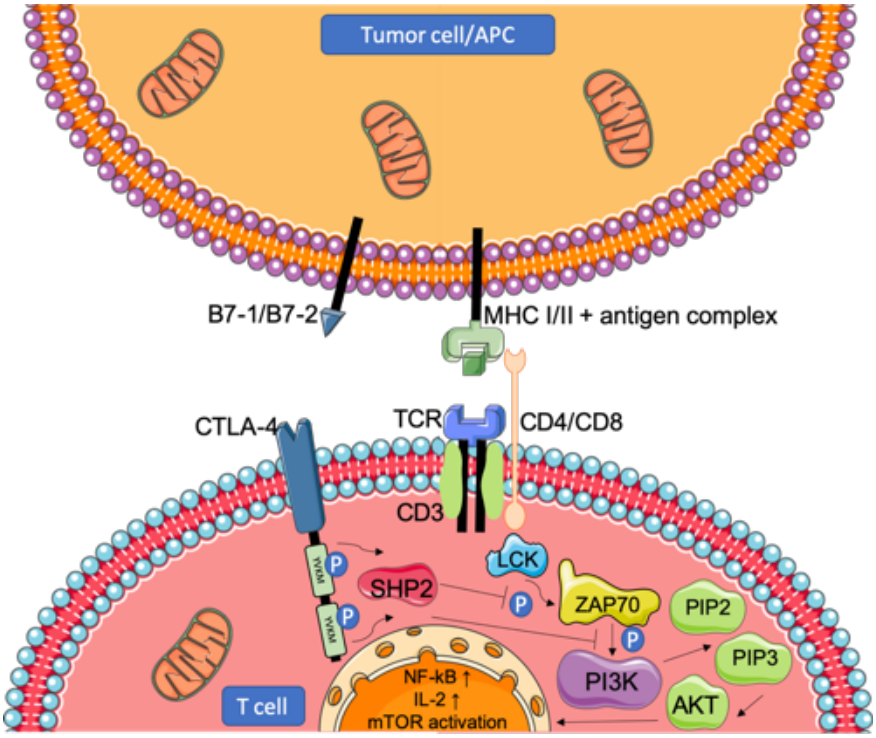
specimens, suggesting that immune evasion is a fundamental step in disease progression.[21]

The pd-1/pd-l1 and the ctla-4/b7 pathways

The discovery of these two signaling pathways resulted in the 2018 Nobel prize in physiology or medicine, awarded to Jim Allison and Tasuku Honjo, for describing the CTLA-4/B7 and PD-1/PD-L1 pathways respectively.[25] There is a great body of evidence demonstrating the key role of these negative regulators in maintaining T cell homeostasis. Mice lacking CTLA-4 expression develop a lethal disease secondary to an extreme increase in polyclonal T cell proliferation that infiltrates different lymphoid and non-lymphoid tissues and organs.[26,27] Deletion of CTLA-4 is also related with the development of systemic autoimmune disorders during adulthood in mice.[28] Similar features have been seen in humans carrying heterozygous germline mutations in the CTLA-4 gene, developing a lupus-like autoimmune entity accompanied by immunodeficiency traits like recurrent infections and hypogammaglobulinemia, as well as tissue infiltration by T cells.[29] PD-1 deficient mice only show marginal lymphoproliferation, but are related with the onset of autoimmune phenomena in early adulthood in mice, showing its importance as a regulator of activation and proliferation of autoreactive T cells.[30]

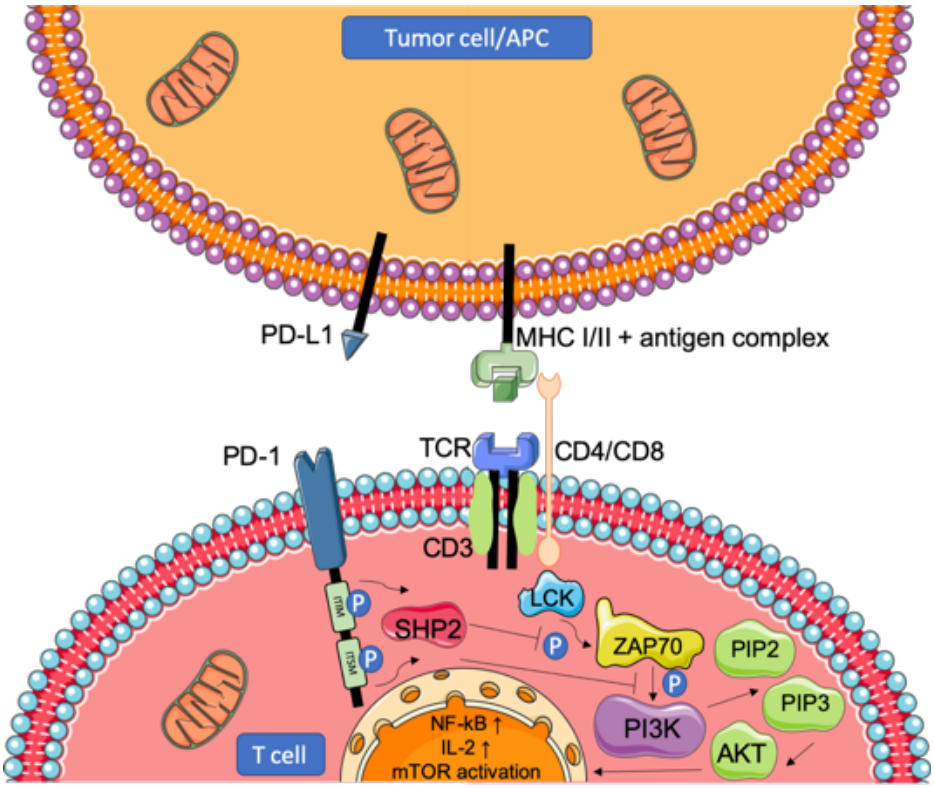
- **Signaling of the CTLA-4/B7 pathway:** For the adaptive immune system to be activated against certain peptide antigens (wherever the origin of this one) Antigen Presenting Cells (APCs) must process antigens and present them in their membranes in form of HLA-antigen complexes to T cells. Class 1 HLA molecules (HLA-1) will interact with CD8+ T cells, and class 2 HLA molecules will interact with CD4+ T cells. During the antigen presentation process, an immunologic synapse is formed, where multiple molecules generate multiple signals, starting from the TCR-HLA-Antigen interaction. Some co-receptor signals are needed for proper T cell activation. First CD40 on the APC surface interacts with CD40L on the T cell membrane, inducing the expression of B7 molecules in the APC (B7-1/CD80 and B7-2/CD86), then the B7 molecules interact with the costimulatory receptor on the T cell surface CD28 whose expression was initiated by TCR signals, after enough activation signals have been performed, CTLA-4 expresses on the activated T cell and competes with CD28 for B7 molecules, with a 20-fold higher affinity. CTLA-4/B7 signaling is inhibitory and it is a critical step in finishing the immunologic synapse. **Figure 1** shows the molecular signaling of this pathway. CTLA-4 is naturally expressed in FOXP3+ CD4+ CD25+ T cells (regulatory T cells or Tregs) as a main effector mechanism of peripheral self-antigen tolerance.

Figure 1. Molecular diagram of intracellular signaling after CTLA-4/B7 interaction



- **Signaling of the PD1/PD-L1 pathway:** programmed cell death 1 (PD-1) (CD279) is a membrane receptor commonly expressed in T cells and a member of the CD28 family of surface receptors, a sub member of the immunoglobulin superfamily. Its putative ligands are PD ligand 1 (PD-L1) (CD274) and PD-L2 (CD273). Common tissues of PD-1 expression are the thymus, lymph nodes, spleen and the bone marrow, CD4-CD8- thymocytes might also express it. The PD-1/PD-L1 pathway plays a key role in peripheral self-antigen tolerance. When PD-1 interacts with PD-L1, phosphorylation of the ITSM motif in the cytoplasmic tail of PD-1 occurs, this phosphotyrosine residue attracts proteins with the SH2 domain, especially SHP1/2 and SH2D1A, which act as phosphatases, inducing the inhibition of the different activation and costimulatory signals, including the TCR signal via ZAP70, and the costimulatory signal of CD28 via PI3K/AKT. **Figure 2** shows the immune synapse emphasizing PD-1/PD-L1 signaling.

Figure 2. Molecular diagram of intracellular signaling after PD-1/PD-L1 interaction occurs



Targeting the immune checkpoints with inhibitory molecules

Different inhibitory molecules have been designed to alter signaling of the above-mentioned pathways, most of them monoclonal antibodies. To the date one CTLA-4 and five PD-1/PD-L1 neutralizing monoclonal antibodies have been approved for the treatment of different cancers. Nivolumab, pembrolizumab and cemiplimab are PD-1 inhibitors, avelumab, durvalumab and atezolizumab are PD-L1 inhibitors and ipilimumab is a CTLA-4 inhibitor.[31–33] Immunotherapy for checkpoint blockade has revolutionized cancer treatment, significantly increasing the survival of certain patients with advanced malignancies. A list of the current available monoclonal antibodies against immune checkpoint and their biologic features are shown in **table 1**.

Table 1. Current immune checkpoint inhibitors approved for various types of cancer

Drug	*Type of drug*	*IgG type*	*Human fraction*	*Commercial name*	*Manufacturing company*
PD-1 targeting					
Pembrolizumab	Monoclonal antibody	IgG4	Humanized	Keytruda	Merck
Nivolumab	Monoclonal antibody	IgG4	Human	Opdivo	Bristol-Myers Squibb
Cemiplimab[34]	Monoclonal antibody	IgG4	Human	Libtayo	Sanofi
Dostarlimab	Monoclonal antibody	IgG4	Humanized	Jemperli	GlaxoSmithKline
PD-L1 targeting					
Atezolizumab	Monoclonal antibody	IgG1	Humanized	Tecentriq	Roche
Avelumab	Monoclonal antibody	IgG1	Human	Bavencio	Merck
Durvalumab	Monoclonal antibody	IgG1	Human	Imfinzi	AstraZeneca
CTLA-4 targeting					
Ipilimumab	Monoclonal antibody	IgG1	Human	Yervoy	Bristol-Myers Squibb
LAG-3 targeting					
Relatlimab	Monoclonal antibody	IgG4	Human	Opdualag	Bristol-Myers Squibb

Renal cell cancer treatment

As occurs in almost all tumors, RCC treatment depends upon disease staging. RCC is commonly staged in local disease (Stages I, II and III) and advanced disease (Stages IV). Treatment depends on the stage disease. These modalities include surgery,[33] targeted therapy,[34] and immune checkpoint blockade.[35] Specifically for local disease is partial or radical nephrectomy.[33,36] Consequently, follow-up must be performed. Different agents, including pazopanib axitinib,[37,38] sorafenib and sunitinib have been tested for adjuvant therapy after treatment in local disease, however, none of them have shown an increased in disease-free survival (DFS) overall survival (OS) and present with statistically significant higher rates of toxicity.[38–40]

Advanced RCC treatment depends on patient risk stratification using the International Metastatic RCC Database Consortium (IMDC) prognostic model,[41] which is presented in **table 2**. Systemic therapy must be initiated as soon as possible when unresectable disease is diagnosed. Initial therapy can be provided using VEGF tyrosine kinase inhibitors or immune checkpoint inhibitors, changing the strategy when relapse occurs. Currently, first-line combinations include one double checkpoint inhibition. For IMDC favourable

risk: nivolumab/cabozantinib, pembrolizumab/axitinib, pembrolizumab/Lenvatinib; and for IMDC intermediate and poor risk: nivolumab/cabozantinib, pembrolizumab/axitinib, pembrolizumab/Lenvatinib, and nivolumab/ipilimumab.[19,42,43]

Table 2. IMDC criteria for survival prognosis after first- and second-line therapy

Criteria	*Risk Profile*	*Median OS after first-line*	*Median OS after second-line*
• Karnofsky performance status < 80%	Favorable (0 points)	43.2 months	35.3 months
•Hemoglobin level below lower limit of normal •Time from diagnosis to treatment < 1 year	Intermediate (1-2 points)	22.5 months	16.6 months
• Corrected calcium above the upper limit of normal • Platelets greater than the upper limit of normal • Neutrophils greater than the upper limit of normal	Unfavorable (3-6 points)	7.8 months	5.4 months

After decades of none advances in RCC treatment, immune checkpoint inhibition arrived to stay and had already taken over the whole treatment of RCC regarding of staging. Immune checkpoint inhibition has demonstrated its efficacy and safety in different phases of RCC treatment. It is now approved as first-line therapy in patients with advanced RCC with intermediate- and poor-risk disease as well as in relapse after antiangiogenic therapy. A table with all the clinical trials who lead to the approval of current immune checkpoint blockade in RCC are shown in **table 3**.

Table 3. Clinical trials who led to the approval of immune checkpoint inhibition for RCC

Sttudy name	*Year of publication*	*Intervention (i*)*	*Control (c)*	*Overall survival (i vs c)*	*Median progression-free survival (i vs c)*	*Reference*
Approved for first-line treatment						
CHECKMATE 214 (Phase III)	2018	Nivolumab plus ipilimumab	Sunitinib	18-month OS of 75% vs 60%	11.6 months vs 8.4 months	Motzer *et al.*[44]
KEYNOTE 426 (Phase III)	2019	Pembrolizumab plus axitinib	Sunitinib	18-month OS of 89.9% vs 72.1%	15.1 months vs 11.1 months	Rini *et al.*[45]
JAVELIN renal 101 (Phase III)	2019	Avelumab plus axitinib	Sunitinib	No significant differences	13.8 months vs 8.4 months	Motzer *et al.*[46]
CHECKMATE-9ER	2021	Nivolumab plus cabozantinib	Sunitinib	12-month OS of 85.7% vs 75.6%	16.6 months vs 8.3 months	Choueiri *et al.*[47]
CLEAR	2021	Lenvatinib plus pembrolizumab	Everolimus	No significant difference	23.9 months vs 9.2 months	Motzer *et al.*[48]
Approved for second-line treatment after antiangiogenic therapy						
CHECKMATE025 (Phase III)	2015	Nivolumab	Everolimus	18-month OS of 52% vs 45%	No significant differences	Motzer *et al.*[49]
Other finished trials						
IMmotion 151	2019	Atezolizumab plus bevacizumab	Sunitinib	No significant differences	11.2 months vs 7.7 months	Rini *et al.*[50]

Conclusions

RCC is usually a tumor resistant to chemotherapy. It is well-known that RCC is a highly immunoresponsive tumor in which immune surveillance is usually addressed to induce anti-tumor responses. Different experimental studies have demonstrated that PD-L1 is expressed in tumor cells as well as in TILs and metastatic cells in patients with RCC. Different combinations of immune checkpoint inhibitors are approved as first-line therapy in patients with advanced RCC with intermediate- and poor-risk disease as well as in disease progression after antiangiogenic therapy. The selection of which treatment combination is based on the treating-physician criteria as no current biomarkers are available

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