REVIEW ARTICLE

Update on pharmacological therapy for advanced kidney cancer

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ABSTRACT

Introduction: renal cell carcinoma is a neoplasm with increasing incidence and mortality worldwide.
Objective: to update the pharmacological treatment of patients with advanced or metastatic renal cell carcinoma and to report on new experimental options.
Methods: a search was carried out in the Medline, Web of Science and other databases, between the years 2018 and 2021 in the Spanish, English, French, German and Portuguese languages. The review was run using the descriptors: kidney cancer, immunotherapy and targeted therapy. Original and review articles, web pages, doctoral and specialty ones and case reports were selected.
Results: targeted therapies are the cornerstone of treatment for advanced or metastatic renal cell carcinoma. Immune checkpoint inhibitors transform your drug treatment and are the basis of most recent research. Adverse events are reported in both options.
Conclusions: investigations are carried out that will provide new options based on combinations of targeted therapies with immunotherapy.
Key words: advanced renal neoplasm; drug therapy

RESUMEN

Introducción: el carcinoma de células renalesconstituye una neoplasia en incremento de incidencia y mortalidad a nivel mundial.
Objetivo: actualizar el tratamiento farmacológico de pacientes con carcinoma de células renalesavanzado o metastásico e informar sobre nuevas opciones experimentales.
Métodos: se realizó una búsqueda en las bases de datos Medline, Web of Science y otras, entre los años 2018 y 2021 en los idiomas español, inglés, francés, alemán y portugués. La revisión se ejecutó con los descriptores: cáncer renal, inmunoterapia y terapia dirigida. Se seleccionaron artículos originales y de revisión, páginas web, tesis doctorales y de especialidad e informes de casos.
Resultados: las terapias dirigidas son el pilar fundamental del tratamiento del carcinoma de células renales avanzado o metastásico. Los inhibidores de puntos de control

inmunológico transformansu tratamiento farmacológico y en ellos se basan la mayoría de las investigaciones recientes. En ambas opciones se informan eventos adversos.
Conclusiones: se ejecutan investigaciones que proveerán de nuevas opciones basadas en combinaciones de terapias dirigidas con inmunoterapia.
Palabras clave: neoplasia renal avanzada; terapia farmacológica

INTRODUCTION

Renal cell carcinoma (RCC) is a tumor arising from renal tubule cells. Until recently it was considered an infrequent neoplasm, but in the last decades its incidence has experienced a striking increase.[1,2]
Kidney cancer accounts for 80 to 85% of malignant renal tumors, is the most aggressive of urological cancers and also represents 3% of adult tumors.[3] The sex ratio is 1.5 males for every female and by age its maximum incidence is between 50 and 70 years of age.[4,5] Globally, RCC is the sixth leading cause of death from cancer and is estimated to be the cause of 95,000 deaths per year worldwide.[6] The overall five-year survival rate varies from 34 to 71%.[7,8] Over the last five decades there has been a steady increase in its incidence, which is around 2 to 4% per year.[3] Several factors may explain this phenomenon: the improvement of imaging techniques with the incorporation and accessibility of ultrasound and computed axial tomography or nuclear magnetic resonance that facilitate earlier detection of the tumor. With these tools the incidental finding of RCC in asymptomatic patients has increased from 13% during the 1970s to 60% in the 1990s.[9] Many of these asymptomatic cases are diagnosed with localized disease, but others are detected with advanced disease, suggesting that there are additional environmental factors influencing the increased incidence.[10,11]
In the past, treatment options for RCC have been extremely limited. Radical surgery is the only effective potentially curative treatment for localized kidney cancer.[12,13] It is also indicated in regionally more advanced stages; for example, in tumors that invade the vena cava or have minimal adenopathic disease.[14,15]
The majority of kidney cancers are resistant to chemotherapy. In some patients the combination of gemcitabine with capecitabine or fluorouracil temporarily reduces tumor size.[16,17] Radiation therapy is not effective as a primary treatment for kidney cancer and is rarely used alone because of the damage it causes to the healthy kidney, it is only used in a patient who cannot undergo surgery and even then it is usually only used in areas where the cancer has spread, not in the primary kidney tumor.[18]
In advanced forms of the disease (stages III and IV according to the American Cancer Society, 2019) radical nephrectomy is preferred. Partial nephrectomy is usually not appropriate, although in selected patients it could be performed if feasible. Once surgery has been performed in many patients with localized RCC, adjuvant treatment is not established; however, in patients with stage III cancer, with clear cell histology and with a high risk of recurrence, some targeted therapy can be administered as adjuvant treatment for one year in order to reduce the risk of recurrence. In stage IV the survival rate is greatly reduced, and the

disease is incurable in many cases, so treatment is mainly based on prolonging the patient's life, as well as improving its quality.
The main objective of this study is to provide an update on current pharmacological treatment in patients with advanced renal cancer, especially in the treatment administered to patients with metastatic disease. Since the treatments used in advanced stages are not usually curative, the aim is to report on new treatments that are currently in the clinical trial phase for patients with this type of cancer.

METHODS

Articles published between 2018 and 2021 were prioritized for this update, except for one from 2017 that was included due to its importance. Articles in Spanish, English, French, German, Portuguese, and French were reviewed. The literature review was executed with the following descriptors: renal cancer, immunotherapy and targeted therapy. A search was performed in the Medline, Web of Science, LILACS and Cochrane Library databases until February 2022; in addition to gray literature sources (clinical trial registries and cancer conferences). A total of 117 articles were identified and selected with the aim of retaining only those that best described the elements of the review, in Spanish and English. Thus, the study was limited to 37 articles: 17 original articles, eight review articles, six web pages, three doctoral theses, two case reports and one specialty thesis.

DEVELOPMENT

Conventional chemotherapy (cisplatin, methotrexate, melphalan, cyclophosphamide, etc.) can produce renal lesions such as acute tubular necrosis and thrombotic microangiopathy, among others. There are other therapeutic options that are directed at a specific target (targeted therapy). This treatment focuses on molecules that are essential for the survival of cancer cells. Its main advantage is the selectivity of the therapeutic target, which differentiates it from chemotherapy and radiotherapy because it does not affect the surrounding healthy tissue, which significantly reduces the risk of adverse events.
Table 1 lists these therapeutic variants, the drugs used to achieve response and their mechanism of action in simple form.after checkpoint inhibitors and targeted antiangiogenic therapies were found to improve outcomes, the combination of these two approaches was studied in clinical trials and shown to result in longer overall survival compared to monotherapy.

A. Targeted therapies

It is one of the main medical treatment modalities for cancer. As a form of molecular medicine it is targeted therapy blocks cancer cell growth by interfering with specific targeted molecules necessary for carcinogenesis and tumor growth, rather than simply interfering with all rapidly dividing cells (e.g., with traditional chemotherapy).

Table 1. Summary of pharmacological treatments for advanced RCC

Types of therapies		Mechanism of action	Drugs
Targeted therapies: block the growth and spread of cancer and interfere with specific molecules or molecular targets	Antiangiogenic therapy	Inhibition of receptor protein kinases	Sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, lenvatinib, tivozanib, and bevacizumab
	Inhibitors of m-TOR	Serine-threonine kinase controlling cell multiplication	Everolimus, temsirolimus
Immunotherapies: strengthen the immune system so that it is able to fight and destroy tumor cells more effectively	Immune checkpoint inhibition (to activate T-cells)	Inhibition of programmed death protein 1 (PD-1)	Niivolumab, pembrolizumab
		PD-1 inhibition by blockade of its ligand.	Avelumab
		ICTLA-4 inhibition that inactivates T cells.	Ipilimumab
	Cytokines	They regulate activation, proliferation and differentiation of various cell types	Interleukin, interferon-α

A.1. Antiangiogenic therapy:

Antiangiogenic drugs are the mainstay of treatment of advanced RCC and their use in recent years has increased survival rates. Their mechanism of action is based on stopping the process of angiogenesis, i.e. the process of formation of new blood vessels from pre-existing capillaries. The most commonly mutated gene in RCC is the VHL gene,[19] this mutation causes an excessive amount of vascular endothelial growth factor (VEGF) to be produced. The binding of VEGF to its receptors (VEGFR), of the tyrosine kinase type, activates various intracellular signaling pathways that lead to the activation of some cellular processes such as angiogenesis and cell proliferation, among others.[20] The increased production of VEGF leads to the neoformation of blood vessels, which has been shown to be essential for tumor proliferation. Angiogenesis inhibitor drugs can block VEFG and thus the angiogenesis process in two ways:

- Inhibiting receptor protein kinases such as VEGFR, fibroblast growth factor receptor (FGFR) or hepatocyte growth factor receptor (MET). The approved drugs with this function are: sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, lenvatinib and tivozanib.
- Through the use of a monoclonal antibody, in this case only one drug is approved: bevacizumab.[20,21]

The mode of action of these therapies is shown schematically in Figure 1.

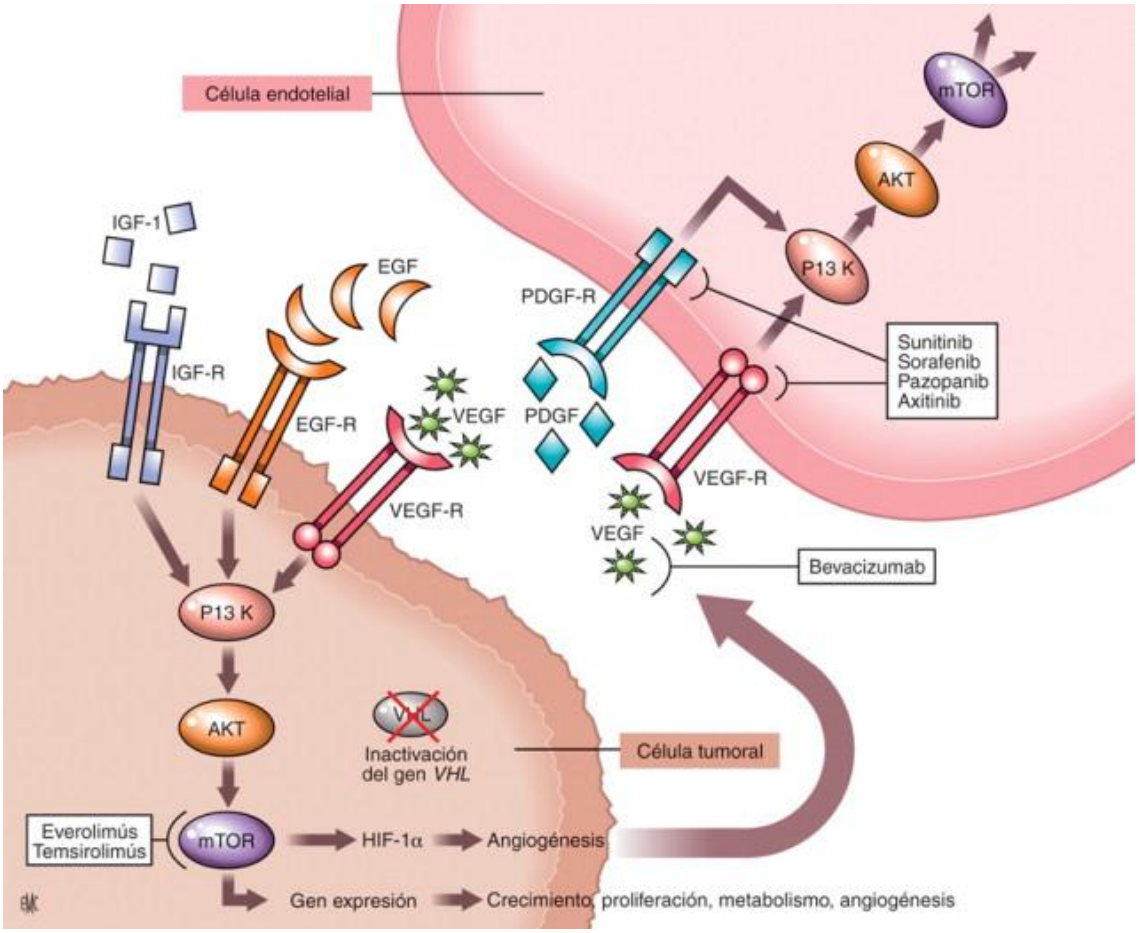

Figure 1. Mode of action of therapies targeting the major molecular pathways of renal cell (clear cell) carcinogenesis: the VHL/hypoxia-inducible factor (HIF)/vascular endothelial growth factor (VEGF) pathway, and phosphoinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian cell target of rapamycin (mTOR).[22]

Sorafenib: a multikinase inhibitor with both antiangiogenic and antiproliferative activity. It was the first VEGF tyrosine kinase inhibitor to obtain Food and Drug Administration (FDA) approval in 2005. It is indicated in the treatment of patients with advanced RCC in whom previous treatment with interferon-α or interleukin-2 has failed or those considered unsuitable for this treatment. The most common adverse effects of this drug are fatigue, diarrhea, increased blood pressure, skin irritations, and hand-foot syndrome (pain, swelling, redness, and blistering of the hands and feet).[23]

Sunitinib: a multikinase inhibitor targeting several receptor tyrosine kinases. It inhibits angiogenesis and cell proliferation, which explains its antitumor activity.[23] It was approved in 2006 in the United States. It is indicated as first-line treatment in adult patients with metastatic RCC and in all prognostic risk groups. It has also demonstrated substantial antitumor activity in second-line therapy of metastatic RCC after progression on cytosine therapy.[24] Common adverse effects of sunitinib include nausea, diarrhea, mouth ulcers, hair or skin color changes, weakness, low white and red blood cell levels, and hand-foot syndrome.[23]

Pazopanib: mechanism of action similar to sunitinib. It is indicated for first-line treatment of metastatic RCC in patients in any of the three prognostic risk groups. Some clinical trials have also shown the efficacy of pazopanib in the second-line treatment of metastatic RCC after previous treatment with cytosines.[24] Both pazopanib and sunitinib are currently the most commonly used treatments in patients with an intermediate or good prognosis.[25] Some of the most common side effects of pazopanib are high blood pressure, nausea, diarrhea, headache, liver problems, and alterations in coagulation and wound healing.[23]

Axitinib: is a potent and selective VEGF receptor inhibitor. It inhibits VEGF-mediated endothelial cell survival and proliferation. It is indicated for first-line treatment of advanced RCC for use in certain circumstances in patients in any prognostic risk group and for second-line treatment after failure of prior treatment with sunitinib or cytosines.[24] As second-line therapy, treatment with axitinib has clearly demonstrated clinical superiority to sorafenib.[23,26] Common side effects of axitinib include high blood pressure, fatigue, nausea, vomiting, diarrhea, poor appetite, weight loss, hand-foot syndrome, and constipation. It is also possible that it may cause the thyroid gland to become hypofunctioning.[23]

Cabozantinib: is a small molecule that inhibits multiple tyrosine kinase receptors involved in angiogenesis, tumor growth and metastatic progression of cancer. It inhibits MET and VEGF receptors, among others. It is indicated for first-line treatment of metastatic RCC in adults of any prognostic risk group and for second-line treatment after treatment with VEGF-targeted therapy.[24] Common adverse effects include diarrhea, fatigue, nausea, vomiting, high blood pressure, hand-foot syndrome, constipation, poor appetite and weight loss.[23]

Lenvatinib: this drug is also a receptor tyrosine kinase inhibitor. It selectively inhibits the activity of VEGF receptors, as well as others such as FGFR and platelet-derived growth factor receptor (PDGF), also related to oncogenic and proangiogenic pathways. It is indicated in combination with everolimus as second-line treatment in adults with advanced RCC.[24] Common adverse effects of Levantinib include diarrhea, fatigue, nausea and vomiting, mouth ulcers, high blood pressure, loss of appetite and weight loss, joint and muscle pain, and swelling in the arms or legs.[23]

Tivozanib: potently blocks all three VEGF receptors, enabling its antiangiogenic and antitumor activity. It has been approved by the European Medicines Agency (EMA) for first-line treatment in adults with advanced RCC. It is also indicated for second-line treatment following cancer progression after cytosine therapy.[24] Tivozanib has been shown to improve progression-free survival (PFS) and response rate versus sorafenib, especially in patients in the good prognosis group.[25,27] The most frequent adverse reactions include hypertension, dysphonia, fatigue and diarrhea.[23]

Bevacizumab: unlike all the previous ones, bevacizumab is a monoclonal antibody. Its mechanism of action consists of binding to the circulating VEGF protein and neutralizing it. This neutralization causes regression of tumor vascularization, normalizes residual tumor vasculature and inhibits tumor neovascularization; thus, tumor growth is inhibited.[28] Currently the only

approved combination is bevacizumab+interferon-α.[29] Side effects caused by bevacizumab include high blood pressure, fatigue and headaches.[23]
Treatment with protein kinase receptor inhibitors has boomed in the last twenty years, irrespective of patient safety considerations. Although the results of effect (survival and objective response) are favorable and are supported by many clinical studies, adverse events are not to be underestimated and occur for all the therapeutic options described, leading to frequent dose adjustments or treatment interruptions.ongoing clinical trials with these target therapies used as monotherapy are few (Table 2) and no new drugs with these mechanisms of action are expected for renal carcinoma.

Table 2. Clinical trials in development on advanced RCC

Code of the study	Phase	Drugs
NCT02950766	1	NeoVax/ipilimumab
NCT04522323	1	MEDI5752+axitinib/lenvatinib
NCT03324373	1	Lenvatinib/everolimus in partial or total cytoreductive nephrectomy
NCT03260504	1	Aldesleukin/pembrolizumab
NCT04518046	1	Sitravatinib/nivolumab/ipilimumab
NCT04495257	1	Nivolumab/ipilimumab/APX005M
NCT03829111	1	Clostridium butyricum CBM 588 probiotic strain/ipilimumab/nivolumab
NCT05122546	1	Cabozantinib/clostridium butyricum CBM 588 probiotic strain/nivolumab
NCT04374877	1	SRF388/pembrolizumab
NCT04691375	1	PY314/PY314+pembrolizumab
NCT05176483	1	XL092/nivolumab/ipilimumab/bempegaldesleukin
NCT03483883	1	Avelumab/gemcitabine
NCT04337970	1-2	Talazoparib/axitinib
NCT04540705	1-2	Bempegaldesleukin+nivolumabaxitinib/cabozantinib+nivolumab
NCT01684397	1-2	Bevacizumab/pazopanib
NCT03172754	1-2	Nivolumab/axitinib
NCT04300140	1-2	Batiraxcept/cabozantinib/nivolumab
NCT04626479	1-2	Pembrolizumab/favezelimab+pembrolizumab/belzutifan
NCT05024214	1-2	Lenvatinib+envafolimab/sunitinib
NCT04322955	2	Cabozantinib/nivolumab/cytoreductive nephrectomy
NCT05215470	2	Nivolumab/ipilimumab
NCT04698213	2	Axitinib oral tablet/avelumab
NCT04090710	2	Ipilimumab+nivolumab/SBRT+ipilimumab+nivolumab
NCT04134390	2	Cabozantinib
NCT04134182	2	Nivolumab/ipilimumab
NCT03991130	2	IL-2/nivolumab
NCT04203901	2	CMN-001/nivolumab+ipilimumab/lenvatinib+everolimus
NCT03138512	3	Nivolumab/nivolumab placebo ipilimumab/ipilimumab placebo
NCT03592472	3	Pazopanib/abexinostat/placebo
NCT04987203	3	Tivozanib/nivolumab
NCT04394975	3	Toripalimab+axitinib/sunitinib

A.2. mTOR inhibitors

The mTOR protein is a serine-threonine kinase with deregulated activity in some human cancers and is more active in some types of cancer cells than in healthy

cells. This protein helps control certain cellular functions, including cell multiplication. Its inhibition allows tumor proliferation to be blocked.[27]

Everolimus: this drug binds to the intracellular protein FKBP-12 and forms a complex that inhibits mTOR, which reduces the activity of several proteins involved in the cell cycle, angiogenesis and glycolysis. Everolimus is a potent inhibitor of tumor cell proliferation and has also been shown to reduce glycolysis in solid tumors. It is indicated as a second-line treatment for advanced RCC, following treatment with other drugs such as sunitinib or sorafenib.[23,24] Common side effects include increased risk of infections, nausea, increased cholesterol and blood sugar levels, diarrhea, fatigue and fluid accumulation.[23]

Temsirolimus: the mechanism of action of this drug is similar to that of everolimus. It is used for first-line treatment of advanced RCC in patients with at least three prognostic risk factors. The most common side effects of this drug are very similar to those caused by everolimus.[23]

The authors point out that there is only one ongoing clinical trial involving an mTOR inhibitor, in this case with everolimus, which is evidence that interest in these therapeutic options is waning. This fact seems to be due to the emergence of newer options, with better safety profile and evidence of therapeutic effect.

B. Immunotherapies

Cancer cells are recognized by immune system cells as foreign and trigger what is known as an immune response in order to destroy them; however, in renal cancer, the immune system's control of tumor generation and proliferation is often dysregulated. These therapies can be very useful because they are based on the use of drugs that reinforce the immune system.[21,23] There are several ways of achieving this objective using immune checkpoint inhibitors (ICIs) or cytokines.

B.1. Immune checkpoint inhibition

Immune checkpoints are proteins on the surface of cells that control the immune response by deactivating T cells until they are needed to stop them from attacking normal cells; however, cancer cells can use these checkpoints to avoid being attacked by the immune system. ICIs are drugs that block immune checkpoints and prevent T cells from being deactivated and attacking cancer cells;[27] however, the action of ICIs can cause the immune system to attack other cells as well, leading to potentially serious adverse effects.[23] A schematic of the mechanism of action of these drugs is shown in Figure 2.

Nivolumab: is a PD-1 inhibitor, binds to PD-1 and blocks its interaction with PD-L1. The interaction of PD-1 with its ligand causes inhibition of T-cell proliferation and cytokine secretion. For this reason, inhibition of this interaction enhances T-cell responses, which will attack tumor cells. Nivolumab is included as a second-line treatment option for advanced RCC.[31] Recently, the nivolumab/ipilimumab combination has been approved as a preferred first-line treatment in patients with advanced RCC in the intermediate and poor prognosis groups. Regarding the use of the nivolumab/ipilimumab combination in the second line of treatment, it has

been shown that this combination is safe and offers a durable response in patients with advanced RCC of all prognostic risk groups.[32]

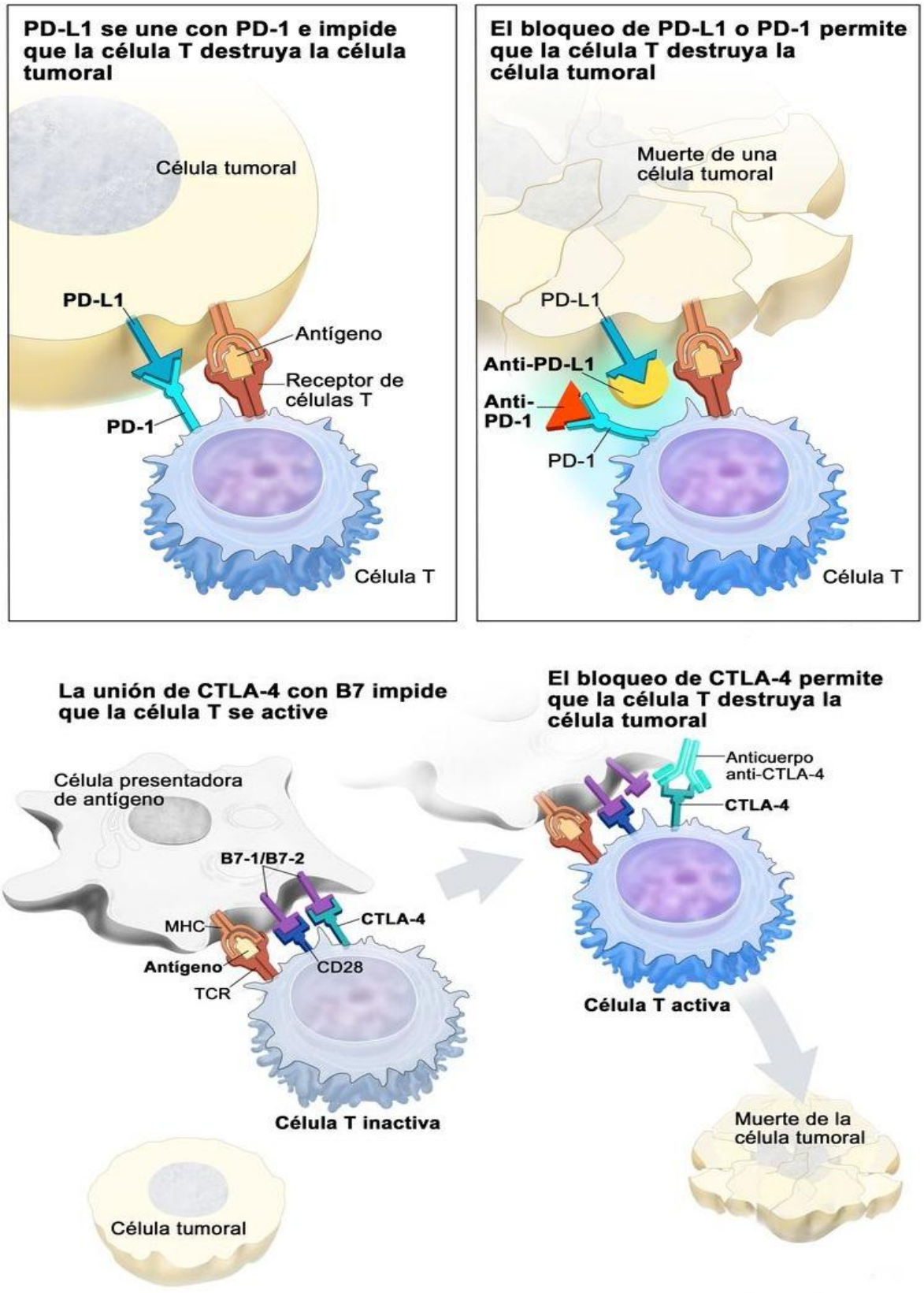

Figure 2. Mechanism of action of PD-1, PD-L1 and CTLA-4 inhibitors[30]

Pembrolizumab: also a PD-1 inhibitor, results have recently been obtained for the combination pembrolizumab/axitinib versus sunitinib. It was observed that disease progression-free survival and response rate were superior when the combination was administered in any of the three prognostic risk groups. Pembrolizumab/axitinib has been approved for use as first-line therapy for RCC.[33]

Avelumab: is a PD-L1 inhibitor and blocks the interaction between PD-1 and its ligand PD-L1, but they make them by binding to PD-L1 instead of PD-1. It is used in combination with axitinib in first-line treatment and some of the most common adverse effects of the combination are fatigue, diarrhea, high blood pressure, cough, shortness of breath and abdominal pain.[34]

Ipilimumab: is a CTLA-4 inhibitor (CTLA-4 is a T-cell surface protein that binds to another protein called B7 protein). This binding causes the T-cells to remain inactive and not attack cancer cells. CTLA-4 inhibitors bind to CTLA-4 and block this binding, activating the T cells, which will destroy the cancer cells. This monoclonal antibody is administered in combination with nivolumab.[31] Some of its most common adverse effects are diarrhea, itching, fatigue or skin rashes.[23]

In the last decade, the development of checkpoint inhibitors has revolutionized the treatment of patients with advanced renal cell carcinoma, they are positioned as a first-line indication and their association with other targeted therapies is being evaluated, which could lead to possible changes in the therapeutic scenario. It would be advisable to perform risk stratifications in patients with advanced renal cancer, who require monotherapy or drug combinations, in order to propose personalized therapies that allow better individual management.

B.2. Cytokines

Cytokines are proteins that regulate and coordinate the behavior of the immune system. They are capable of enhancing antitumor activity and are therefore used to treat cancer. Interleukin-2 and interferon-α are examples of cytokines used in immunotherapy. Cytokines such as interferon-α and high-dose interleukin-2 (Il-2) have been shown to have clinical efficacy since the 1990s to treat metastatic RCC; however, both drugs offer benefits to a small group of patients (those with favorable disease biology) and are also associated with high toxicity, especially in the case of high-dose Il-2.[20] Currently their use has been displaced by new treatments with greater efficacy and lower toxicity.

Interleukin-2: this is a cytokine produced by T lymphocytes and its use in high doses had been the mainstay of therapy for metastatic CRC until the appearance of VEGF inhibitors in 2005.[35] It is currently administered intravenously to highly selected patients in centers that have experience with this type of treatment.[24,27] High doses of Il-2 produce a large number of side effects: extreme tiredness, low blood pressure, fluid accumulation in the lungs, shortness of breath, heart attacks, kidney damage, intestinal bleeding, mental changes, high fever and chills, among others.[23]

Interferon-α: IFNs were the first endogenous regulators with a demonstrated anti-angiogenic action. Type I IFNs negatively regulate the expression of pro-angiogenic molecules such as fibroblast growth factor (bFGF), interleukins (IL)-8

and matrix metalloproteinases (MMP)-2 and MMP-9.[36,37] IFN-α blocks CSF-1-promoted monocyte division,inhibits PDGF-mediated signal translation in fibroblasts and reduces EGFR expression and VEGF expression.[38,39] It is currently used in the first-line treatment of advanced CRC in combination with bevacizumab.[24]

Cytokine therapy was initiated more than 20 years ago and is the only treatment available until 2005; it raised high hopes and achieved objective responses in about 20% of patients with metastases, but its objective response rate is low. Research with these products is practically non-existent, although the authors consider that they should be resumed due to the high costs of other therapies and evidence that the results obtained in clinical research often do not correspond to those generated in routine medical practice. A variant would be polytherapy with some of the drugs listed above.

Clinical research

The number of clinical trials underway to treat advanced CRC, especially with numerous drug combinations, is remarkable. Table 2 shows some examples with drugs that have already been described.[27]

When these investigations are concluded, a new scenario for the treatment of advanced or metastatic renal cancer will have been shaped, perhaps a step closer to the personalized medicine so longed for by patients; however, the sometimes privative prices of these pharmacological variants must be considered.

Since 2011, a research project to evaluate the effectiveness and safety of the application of a combination of interferons in patients with renal tumors in advanced stages has been carried out at the "Arnaldo Milián Castro" University Clinical Surgical Provincial Hospital of Santa Clara City, Villa Clara Province. To date, the results have been favorable and have led to consider this pharmacological variant as a possible new line of treatment in the future.

CONCLUSIONS

The use of targeted therapies is the mainstay of treatment of advanced or metastatic RCC and their implementation has led to increased survival. Immune checkpoint inhibitors are transforming the pharmacological treatment of RCC and have been the mainstay of most of the research in recent years; both therapeutic options are not risk-free because more or less intense adverse events have been reported in all the pharmacological variants described. Numerous clinical trials are underway that will provide new therapeutic tools for the disease in the future, especially with regard to combinations of targeted therapies with immunotherapy.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.