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Biomarkers and new therapeutic targets in renal cell carcinoma

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Abstract. – OBJECTIVE: Renal Cell Carcinoma (RCC) is the most common malignancy in adult kidneys. The American Cancer Society estimated 62,700 new cases and 14,240 deaths in 2018. Although early detection has improved in recent years, the treatment remains a challenge and reliable biomarkers for poor outcomes become necessary for the prevention of metastases and improve the quality of patients' life during and after treatment. Then, the current status of the search for new RCC biomarkers was discussed, as well as the latest discoveries in the RCC risk and metastatic treatment were discussed in this review.

MATERIALS AND METHODS: Extensive research was carried out in the online databases and full-free text articles published in the last 5 years, or more when convenient, were evaluated. Articles were included that addressed the proposed theme and were published in the English language.

RESULTS: The present state of knowledge on biomarkers for RCC carcinogenesis and progression is still much to be understood about RCC risk factors and molecular pathways resulting in metastatic progression. Newest RCC target therapies were discussed, mainly in relation to immunological therapy, and vaccines that have been tested in numerous trials with different cancer types.

CONCLUSIONS: The development of targeted therapies has revolutionized the treatment of advanced and metastatic cancers or non-responder patients. Combined therapy between classical chemotherapy and adjuvant immunotherapies has been modifying the cancer patients prognosis and bringing the hope of a cure in many cases.

Key Words
Renal cell carcinoma, Incidence, Biomarkers, Therapeutics targets, Immunotherapy

Introduction

Renal cell carcinoma (RCC) is the most common malignancy in adult kidneys[1,2], accounting for 90-95% of cancers at this organ[3]. RCC represents 2-3% of all cancers in adults[2,4-6], and is the third most common type of genitourinary malignancy after prostate and bladder cancers[3], and is the seventh most common cancer in men and the ninth most common among women[5].

Due to the kidney compensation mechanisms[3] and the RCC asymptomatic nature in the initial phase, more than one third of patients present at diagnosis time a locally advanced tumor or a metastatic disease[1]. These stages may be painless and therefore undetected[7]. Almost half of all kidney tumors are discovered incidentally[4,8], and only a minority (6-10%) of patients present with the classic triad; flank pain, hematuria, and palpable abdominal mass[4]. Patients, who exhibit a clinically confined disease, usually undergo a curative nephrectomy with 70-80% of 5-year survival rates[8],

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being the only curative option for many patients with localized disease[9], because RCC is generally resistant to chemotherapy, radiation therapy or hormone therapy[10].

The clinical course of localized clear cell RCC (ccRCC) can at times be difficult to predict, even in patients who have similar clinical-pathological parameters in tumor grade and stage, presence of vascular and capsular invasion[11]. However, up to 40% will have secondary tumors in distant sites[11]. Surgical resection of RCC metastatic tissue supposedly improves the patients' outcome, and 5-year survival rates are between 35% and 50% after surgical treatment for solitary metastasis[7,12], and the survival rate after 5 years is only 9%[7]. Untreated RCC patients with metastasis showed a median survival of 6-12 months and 5-year survival rate of less than 20%[2].

The search for reliable biomarkers is a main goal in oncology, thus the need for early diagnosis, accurate identification of histologic type, prediction of response to treatment, chance to develop metastasis or recurrence are urgently necessary. For RCC, the identification of accurate molecular/expression profile which can provide biologically critical pathway information may be valuable for predicting outcomes and treatment responses[11].

In this review, general information will be provided about the current status of biomarkers and new developed therapies or under development for the RCC treatment. The discussion will highlight the main findings from previous studies to examine the feasibility of biomarkers utilization in predicting aggressiveness, therapeutic response and survival in RCC patients, in addition to bringing new therapeutic discoveries for the treatment of localized and metastatic RCC. The review will conclude with a discussion of future prospects in the patients care with resistant RCC. We would like to present a comprehensive and summarized of current information in this field. We used Medline to identify studies with information about biomarkers, and therapy targets in renal cell carcinoma.

Materials and Methods

Extensive research was carried out in the online PubMed, MEDLINE, Scielo databases and full-free text articles published in the last 5 years, or more when convenient, were evaluated. Articles were included that addressed the proposed theme and were published in English language. The terms MeSH (Medical Subject Headings) used for the research were the following: "Renal Cell Carcinoma" and "RCC", "RCC biomarkets", and "RCC therapeutic targets". The most relevant literature on RCC was summarized between 2013 to February 2018.

Inclusion criteria, exclusion criteria and selection of data extraction were: (1) articles published in English from 2013 to February 2018, (2) studies in patients with RCC, and (3) studies approved by the Ethics Committee. Revisions about RCC were included in addition to the original articles. Methodological aspects were not used as inclusion criteria, since the objective was to perform a survey of the literature on RCC. Studies that presented methodological deficiencies, such as small samples, were considered. All studies that did not include RCC patients were excluded.

Results

Incidence and Survival

The current world incidence of RCC is approximately 5.8 per 100,000 individuals[4], and has increased, due to an aging population[5], and the increased use abdominal imaging diagnostics[8,13] (Figure 1[13]). RCC has registered an annual increase of about 2-3% in incidence[4,8,11]. In the US, about 62,700 cases of RCC will be diagnosed and 14,240 patients will die due to this disease in 2018[14].

RCC is the most lethal urologic malignancies[4,15], with the highest mortality rate among genitourinary cancers[16]. Some modifiable risk factors for ,RCC are well established, including smoking, obesity and hypertension, as well as physical inactivity, occupational exposure to trichloroethylene and a history of diabetes mellitus[17,18]. Genetic background also presents differences in response to surgical therapy and medical prognosis[2].

RCC is composed of a group of tumor types, representing a heterogeneous and complex family which is composed of several different subtypes, such as clear cell (ccRCC), papillary (pRCC) and chromophobic (chRCC), which originate from the renal tubular epithelium[10]. Particularly in renal parenchyma, the ccRCC is the most common histologic subtype[12] comprising about 70-80% of RCC tumor cases[16], and over 90% of deaths[11].

RCC has been well described by its tendency to metastasize, occurring in about one third of patients at time of diagnosis[2,6,9,19,20] when the patient

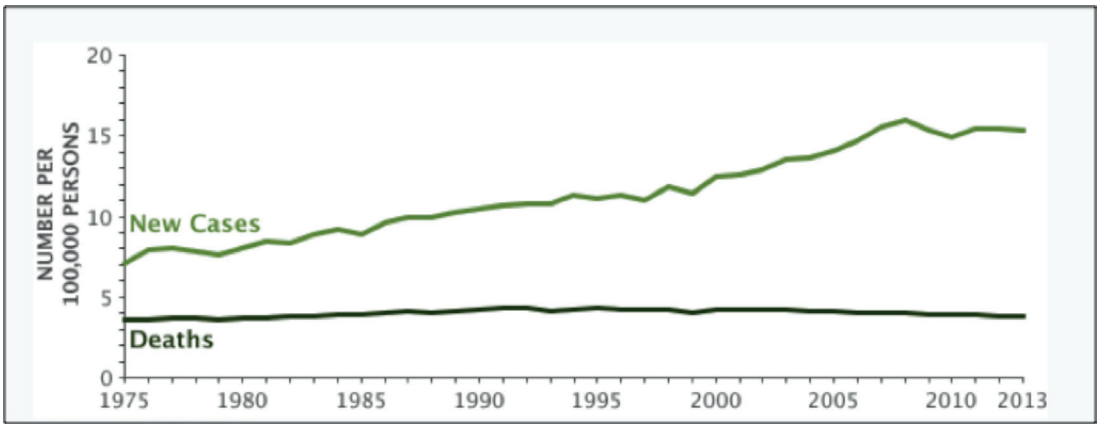

Figure 1. New cases, and Death, SEER 9 Incidence & U.S. Mortality 1975-2013, All Races, Both Sexes. Rates are Age-Adjusted. (National Cancer Institute. Surveillance, Epidemiology, and End Results Program, SEER. seer.cancer.gov)[13].

will eventually develop distant metastasis[2,6,9], despite the primary tumor treatment [3]. The risk for recurrence is higher in the first three years after radical nephrectomy[7]. The average survival following RCC metastatic, is about 4 months[3] with a survival rate of only 10% to 20% in 2 years[9], being the survival rate less than 10% in 5 years[1,10].

Survival rates are directly correlated with the stage and tumor size, demonstrating the importance of early detection when the lesions are small[8]. The genetic predisposition to RCC is currently estimated to be present in 3-5% of RCC patients, often showing recognizable others features in addition to the increased risk of RCC[4]. RCC patients should be under surveillance for detecting progression or recurrence at regular intervals by imaging, often computed tomography scan after surgical treatment[8]. Therefore, a regular annual check-up is advisable in such cases after radical nephrectomy[7].

Despite a revolution in currently available targeted therapies and now immune checkpoint inhibitors, metastatic RCC remains highly chemotherapy[9], hormone therapy and radiotherapy resistant, and treatment of metastatic RCC remains ineffective[7], although a small fraction of patients have long-lasting responses for interleukin 2 (IL-2) immunotherapy[8]. Currently, combination therapy including surgery and therapy target provides the best opportunity for palliation and healing[7].

RCC Biomarkers

In order to use biomarkers in a standard practice, they should endure a rigorous evidence-based analysis and be validated in large clinical trials[21]. Numerous recent studies have proposed tentative biomarkers for RCC, but these clinical utilities have not been proven yet. The current RCC treatments were mostly based on the histological type. This approach has not demonstrated an acceptable efficacy in the patient management. Therefore, new biomarkers are necessary for a better prediction of outcomes and prognosis. Currently, several predictive prognostic parameters for RCC have been established, including Classification of Malignant Tumors (TNM) Stage, Fuhrman grade, histological subtype, and clinical parameters such as the Eastern Cooperative Oncology Group performance status, level of hemoglobin, and lactate dehydrogenase levels. The nomograms development that include different variables, with better discriminators and more refined criteria will improve patients care and provide a more accurate prediction tool for prognosis of RCC patients[21].

Although genetic factors explain only 5% of all RCC cases, investigated genetic biomarkers have provided insights into the molecular pathogenesis of both familial and sporadic RCC cases. One of the examples is the Von Hipple-Lindau (VHL) Syndrome, a dominantly inherited multisystem familial cancer syndrome associated to ccRCC, as the somatic inactivation of the VHL tumor suppressor gene is the most frequent event in the evolution of sporadic ccRCC[22]. The Birt–Hogg–Dube syndrome, is another dominantly familial cancer syndrome associated with RCC susceptibility, results from inactivating mutations in the folliculin gene, where patients show loss of the wild-type allele of tumor suppressor gene[22].

Gene deregulation in RCC has been extensively studied through techniques such as genomics,

proteomics, cytogenetic, studies of sequencing and gene or microRNA expression, among others[16]. These studies have provided useful insights into RCC biology and its clinical presentation and have led to an increased understanding of the RCC heterogeneity which greatly influences in the therapeutic decisions[16]. The advances in the genetics, as well as in the genomics fields including the Cancer Genome Project, has been changing the paradigms in oncology, improving the patients' diagnostic and treatment with cancer[21].

Numerous gene altered regulations have already been observed in RCC, as silencing, methylation, overexpression, downregulation, mutation, and translocation genes, besides the miRNAs differential expression in the different types of RCC. The majority of sporadic ccRCC's emerge from loss of function by mutations or biallelic hypermethylation of the VHL gene[11]. Despite the recent findings on renal oncogenesis, little is known about the sequence of genetic effects that occurs in most histological types of RCC after the initiating event, which is the loss of the VHL tumor suppressor gene, and its tumorigenesis[15]. The VHL gene is located at chromosome 3p25-26 and encodes for a tumor suppressor protein, pVHL. The cellular hypoxia is a critical stimulus for carcinogenesis and progression. The cellular hypoxia activates many transcription factors such as hypoxia inducible factor-1 (HIF-1), which is degraded by pVHL[20]. RCC patients with mutations in pVHL gene have a poor prognosis. Hypermethylated or mutated pVHL gene may have a reduced prolyl hydroxylase activity. Then, an up-regulation of the HIF-1α increases transcription of factors related to cellular proliferation, angiogenesis and metastasis, and other hypoxia-inducible genes such as transforming growth factor-β, vascular endothelial growth factor (VEGF), and Platelet-derived growth factor (PDGF)[20,23].

Increased expression of nuclear HIF-2α was correlated to small tumors, and, on the other hand, high HIF-2α concentration in the cell cytoplasm was correlated to distant metastasis, establishing a role of tumor promoter[23]. Kroeze et al[24] reported that clinical stage, tumor size, metastasis and HIF expression were significantly correlated to overall survival using 100 ccRCC patients. In addition, low expression of nuclear HIF was a significant independent prognostic factor for poor outcomes (p=0.009)[24]. Defective VHL gene is founded in approximately 60% of ccRCC patients, and this has a very large implication in the VHL molecular mechanisms [25]. VHL is the gene that exhibits most of the mutations in RCC patients and, when the gene is inactivated, there is an increase in the synthesis of HIF-2α that restores tumorigenesis in VHL-reconstituted ccRCC cells[26]. Therefore, it seems that HIF-2α acts as an oncoprotein while HIF-1α acts as a tumor suppressor[26].

Much interest has focused on the mammalian target of rapamycin (mTOR) signaling pathway as a suitable drug target for the treatment of advanced RCC. Distinct signaling cascades such as the epidermal growth factor receptor/ extracelular signal-regulated kinases (EGFR/ERK), and phosphoinositide 3 kinase/ Protein kinase B (PI3-K/ Akt) pathways are known to converge to the mediated phosphorylation by mTOR, modulating cell growth, the migration and invasion, and are also associated with ribosomal biogenesis, as well as they bind to and inactivate the translation initiation factor Eukaryotic translation initiation factor 4E (eIF4E)[11]. Overexpression of the eukaryotic translation initiation factor 4E-binding protein 1 (eIF4E-BP1) inactivated phosphorylated forms, a biomarker of the mTOR pathway, for the prediction of disease progression in various cancers, including ovary, brain, and prostate cancers. Moreover, these biomarkers panel identified a patient subgroup with aggressive disease who exhibited poorer disease-free survival, representing a biologically relevant molecular signature in ccRCC for the disease progression prediction. An univariate survival analysis suggested that ccRCC patients with both expression of p4E-BP1 and eIF4E had a significantly shorter survival of 2.9 *vs.* 5.7 years as compared to patients with only one, or neither expression (p<0.001). Results from Cox-regression analysis confirmed this trend, thus, expression p4EBP1 and eIF4E increase a Hazard Ratio of 4.2 (CI = 2.1-8.6; p<0.001)[11]. In addition, mutational aberrations in the mTOR/Tuberous sclerosis 1 (TSC1) pathway may have predictive value in the choice of systemic therapies[27].

It has been suggested that the epidermal growth factor-like domain multiple 7 (EGFL7) has an important function in the RCC growth by facilitating angiogenesis. EGFL7 seems to be necessary in RCC vascular tubulogenesis through the epidermal growth factor receptor-focal adhesion kinase (EGFR-FAK) signaling activation. In human dermal microvascular endothelial (HMEC-1) cells, the FAK phosphorylation level is significantly induced by recombinant human EGFL7 protein, thereby demonstrating that vascular tubule formation can be disrupted by the EGFL7 downregulation expression[5].

Another tentative biomarker for ccRCC is Ubiquitin Protein Ligase E3C (UBE3C) that was demonstrated as a marker for tumor growth and metastasis. Patients with high UBE3C expression in tumor is associated with significantly worse postoperative survival ($p<0.001$) as compared to the patients with low UBE3C expression[12]. An activation of Wnt signaling pathway (Wnt)/β-catenin by UBE3C leads to migration and proliferation of the ccRCC cell. Over-expression of UBE3C in tumor is correlated with clinical stage and may cause β-catenin nuclear accumulation[12].

Many previous studies investigated a set of immune histochemecal biomarkers including vimentin, Antigen KI-67 (Ki-67), gelsolin, carbonic anhydrase (CA)IX, CAXII, Epithelial Cell Adhesion Molecule (EpCAM), p53, and Phosphatase and tensin homolog (PTEN)[21]. Pantuck et al[28] reported a critical role of PTEN loss and phos-Akt overexpression in RCC progression. In addition, the elevation of phos-Akt cytoplasmic expression and reduction of its expression in the nucleus are inversely correlated with survival among RCC patients[28]. Bui et al[29] demonstrated that both low expression of the CAIX and high expression of the Ki-67 were negative predictors in ccRCC survival[29]. The Ki-67 protein up-regulation is associated with cellular proliferation in primary tumor tissues, overall survival, cancer-specific survival, and recurrence-free survival in patients with RCC[30].

Jacobsen et al[31] reported that the RCC tumor size and TNM stage seems to correlate with the VEGF expression. Further the authors found that VEGF overexpression was a negative predictor for patients' survival[31]. Kluger et al[32] analyzed ccRCCs and pRCC tissue microarrays, using a quantitative analysis of VEGF and VEGF receptor expression by IHC fluorescent and found that high expression of VEGF and VEGF receptors was associated with poor patients' survival[32]. Mutations in VEGFR-3 gene in tumor tissue can be considered as a RCC prognosis biomarker[33].

Lidgren et al[34] revealed that HIF-1α over-expression was associated with a poor ccRCC[34] outcome. Likewise the over-expression of cytoplasm HIF-2α is correlated with distant metastasis[23]. Migita et al[35] found that loss of p27 expression is an independent prognostic factor of poor disease-specific survival[35].

Recently, novel genes and other molecules have been demonstrated as potential molecular biomarkers involved in the RCC carcinogenesis. Studies have shown that mutations in the Reelin (RELN) gene, a cytoskeletal protein, and Forkhead box protein C2 (FOXC2) are generally associated with patients with metastasis. Ahn et al[36] demonstrated that mutations in FOXC2 and CAP-Gly Domain Containing Linker Protein Family Member 4 (CLIP4) led to a significantly increased in cell migration and viability[36]. Protein polybromo-1 (PBRM1), Myeloid/Lymphoid or Mixed-Lineage Leukemia 2 (MLL2), Zinc Finger Protein (ZNF) 536 genes were also mutated more frequently in patients with metastasis[36]. Therefore, mutations in the PBRM1, BRCA1 associated protein 1 (BAP1) and lysine demethylase 5C (KDM5C) tumor genes can be considered in RCC poor prognostic biomarkers, as well as ATP binding cassette subfamily B member 1 (ABCB1) and VEGFR-3 polymorphisms in germline cells, and variations in IL8 levels, or some miRNA[33]. In addition, the up-regulated miR-210-3p, which can be detected in the ccRCC patients' urine at the time of surgery, is a potential non-invasive biomarker[37]. Other genes also associated with renal cell carcinoma in general being validated are receptor tyrosine kinase (MET) proto-oncogene, folliculin (FLCN), Transcription Factor Binding to IGHM Enhancer 3 (TFE3), Transcription Factor EB (TFEB), melanogenesis associated transcription factor (MITF), fumarate hydratas (FH), succinate dehydrogenase complex iron sulfur subunit B (SDHB), succinate dehydrogenase complex iron sulfur subunit D (SDHD), SET domain containing 2 (SETD2), and Jumonji AT-rich interactive domain 1C (JARID1C)[26].

There is currently no reliable ccRCC predictive biomarker[26]. Therefore, new molecular biomarkers are urgently necessary to improve the prognosis and assist in the most appropriate therapeutic choice for RCC. A list of potentials renal cell cancer biomarkers can be found in Table I[5,8,10-12,15,20,22,28,29,31,33,35,38-56].

Therapeutic Targets

As the RCCs are, mostly clinically silent, the diagnosis is performed with advanced or metastatic local tumors. The difference in prognosis between early and advanced disease is enormous, and the 5-year survival rate was 92% for localized diseases, 65% for regional disease (disseminated to the lymph nodes), and 12% for diseases metastatic[13]. Based upon the Leibovich and UISS validated risk scores, high-risk patients have a 2-year local or systemic failure rate of 57.5% and a 3-year metastasis-free survival rate of just 37.1%[19].

Table I. Potentials renal cell cancer biomarkers.

	Samples	Result	Authors
Cancer Predisposition			
Karnofsky Status	118 patients	< 80%	Eggener et al[38]
Karnofsky Status	353 patients	< 80%	George et al[39]
Obesity	> 3,700,000 patients	BMI ≥ 30 kg/m²	Van der Zanden[33]
Nephrectomy	118 patients	< 12 Mo	Eggener et al[38]
Nephrectomy	353 patients	< 12 Mo	George et al[39]
Risk Biomarkers			
Calcium	118 Serum	> 10 mg/dL	Eggener et al[38]
Hemoglobin	118 Serum	< sex-time	Eggener et al[38]
Hemoglobin	353 Serum	< sex-time	George et al[39]
Lactic dehydrogenase	118 Serum	> 1.5 times	Eggener et al[38]
Diagnostics Biomarkers			
BFGF	GSE6344 cells	Overexpression	Zhai et al[40]
Caspase 3/7	UOK257-FLCN^{null} cells	High activity	Lu et al[22]
Cyclic-AMP	FH-deficient cells	Overexpression	Boettcher et al[41]
ES	Nude Mice	Overexpression	Feldman et al[42]
FH	Tumor tissues, 786-O, A498, RCC4, ACHN cells	Low expression	Sudarshan et al[15]
FH	UOK268 cells	Loss activity	Yang et al, 2012[43]
FH	HEK293T cells	Low expression	Boettcher et al[41]
FH	Epithelial kidney Fh1$^{fl/fl}$ mice cells	Overexpression	Frezza et al[44]
HIF-2α	VHL-deficient 786-O, A498 cells	Overexpression	Sudarshan et al[15]
HIF-1α	UOK261 cells	Overexpression	Yang et al[43]
HIF-1	GSE6344 cells	Overexpression	Zhai et al[40]
DNA methylation	Tumor tissues	Decreased	Lasseigne et al[8]
PDGF receptor	GSE6344 cells	Overexpression	Zhai et al[40]
Porphyrins	Epithelial kidney Fh1$^{fl/fl}$ mice cells	Overexpression	Frezza et al[44]
VEGFR	GSE6344 cells	Overexpression	Zhai et al[40]
Prognostic Biomarkers			
Acetyl-CoA carboxylase	446 Tumor tissues	Overexpression	TCGA[45]
AMPK	446 Tumor tissues	Low expression	TCGA[45]
ANXA 2	UOK261 cells	Overexpression	Yang et al[10]
B7-H1	298 Tumor tissues	Expression	Krambeck et al[46]
B7-H1	306 Tumor tissues	Expression	Crispen et al[47]
B7-H4	259 Tumor tissues	Expression	Crispen et al[47]
CAIX	321 Tumor tissues	Low expression	Bui et al[29]
CD57+	120 Tumor tissues	Low expression	Rathmell et al[48]
cIAP1	104 Tumor tissues	Overexpression	Crispen et al[47]
CRP	100 Serum	Overexpression	Rathmell et al[48]
CX3CR1	78 Tumor tissues	Overexpression	Yao et al[49]
CXCR3	154 Tumor tissues	Low expression	Crispen et al[47]
Docosahexaenoic acid	112 Serum	Low expression	Tasaki et al[50]
EGFL7	HMEC-1, 786-0 cells	Overexpression	Xu et al[5]
EIf4E	135 Tumor tissues	Overexpression	Campbell et al[11]
ESR	1075 Serum	Overexpression	Rathmell et al[48]
FABP7	60 Tumor tissues	Overexpression	Zhou et al[51]
GLI 1 and GLI 2	HK-2, 786-O, 769-P cells	Overexpression	Zhou et al[52]
Glutamine transporter	446 Tumor tissues	Up-regulation	TCGA[45]
HIF-1α	92 Tumor tissues	Overexpression	Lidgren et al[34]
HSC71	20 Serum	Overexpression	Zhang et al[53]
IMP-3	371 Tumor tissues	Overexpression	Crispen et al[47]
Iron	SN12C cells	Low expression	Josson et al[54]
Kappa B	786-0 cell	Overexpression	Morais et al[20]

Continued

Table I (cont). Potentials renal cell cancer biomarkers.

	Samples	Result	Author
Prognostic Biomarkers			
Ki-67	321 Tumor tissues	Overexpression	Bui et al[29]
Neutrophil	120 Blood	Overexpression	Rathmell et al[48]
p27	67 Tumor tissues	Low expression	Migita et al[35]
p53	193 Tumor tissues	Overexpression	Crispen et al[47]
p53	HEK 293, Caki-1, Caki-2, A498 cells	Overexpression	Zhou et al[55]
Pentose phosphate pathway	446 Tumor tissues	Up-regulation	TCGA[45]
Phos-AKT nuclear	375 Tumor tissues	Low expression	Pantuck et al[28]
Phos-AKT citoplasmic	375 Tumor tissues	Overexpression	Pantuck et al[28]
Phos-4E-BP1	135 Tumor tissues	Overexpression	Campbell et al[11]
Phos-ATM S1981	HEK 293, Caki-1, Caki-2, A498 cells	Overexpression	Zhou et al[55]
Phos-S6k	375 Tumor tissues	Overexpression	Pantuck et al[28]
Pontin	20 Serum	Overexpression	Zhang et al[53]
PTEN	375 Tumor tissues	Low expression	Pantuck et al[28]
PTEN	446 Tumor tissues	Low expression	TCGA[45]
PUMA	HEK 293, Caki-1, Caki-2, A498 cells	Overexpression	Zhou et al[55]
Reptin	67 Tumor tissues	Overexpression	Ren et al[56]
Survivin	298 Tumor tissues	Overexpression	Krambeck et al[46]
Survivin	670 Tumor tissues	Overexpression	Crispen et al[47]
UBE3C protein	297 Tumor tissues	Overexpression	Wen et al[12]
VEGF and VEGFR-R	229 Tumor tissues	Overexpression	Jacobsen, et al[31]
β-Catenin protein	297 Tumor tissues	Overexpression	Wen et al[12]

Radical nephrectomy is the main treatment choice for localized and non-metastatic RCC, preserving the other kidney[16]. When both kidneys are affected by the disease, partial nephrectomy is performed[20]. Radiotherapy is poorly effective in RCC when compared to other tumors[57], being associated with the development of many side effects. Nephropathy radiation is well recognized to be capable of causing renal injury[20]. RCCs are commonly resistant to conventional chemotherapy[54], whereas, almost all chemotherapeutic agents are ineffective against metastatic RCC[20], as well as show a rather limited response to immunotherapy[2]. Even in patients who undergo nephrectomy without metastasis, the appearance of late metastasis is frequent, demonstrating refractory to current treatments[5,16]. The advanced RCC treatment has been a challenging task for the clinicians[2,20].

In 1990s, a lot of chemotherapeutic agents were examined for RCC treatment; however, all had remission rates less than 15%. Thereafter, the knowledge on molecular pathways involved in RCC increased dramatically, leading to the synthesis of new chemotherapeutic agents, called targeted therapy, such as multiple tyrosine kinase inhibitors, mTOR, kinase inhibitors, monoclonal antibodies and a second generation of taxanes[20]. Recently, Food and Drug Administration (FDA) has approved several therapeutic agents targeted to the new RCC cancer molecular pathways discoveries, such as bevacizumab (Genetech, San Francisco, CA, USA), temsirolimus (Pfizer, New York, NY, USA), sorafenib (Bayer, Leverkusen, Germany), sunitinib (Pfizer, New York, NY, USA), everolimus (Novartis, Basel, Switzerland), and pazopanib (Novartis, Basel, Switzerland)[25].

Sunitinib, sorafenib, and pazopanib are tyrosine kinase (TKIs), vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) pathways inhibitors, oral route, are the first choice and routinely used in the RCC treatment[57]. Temsirolimus and everolimus are rapamycin inhibitors (mTOR), which also participate in the VEGF expression and HIF regulation. Lastly, bevacizumab neutralizes VEGF and prevents its binding to the receptor; it is a monoclonal antibody[9]. Oral sunitinib is currently the most used vascular growth factor inhibitor for the initial treatment of metastatic ccRCC, but in developing countries, it is unaffordable due to the high cost involved[7]. These new targeted agents showed an impressive anti-tumor efficacy and prolongation of the patient's survival with disease progression-free[2].

The use of targeted therapy before or after metastases site treatment was recently published[2,19]. The patient first receives a systemic therapy followed by nephrectomy and reviewed for the various disease stages in RCC[19]. This strategy has been recommended for patients with large tumors that make difficult the initial resection to be performed or those with numerous metastases[9,15]. Many patients have large tumors, so surgical removal is compromised. Therefore, the primary tumor reduction through neoadjuvant therapy has been recommended in tumor reduction, therefore facilitating the nephron-sparing surgery[19].

For these reasons, the utilization of systemic therapy followed by surgery has represented the best therapeutic strategy for patients with advanced disease[9]. High-risk patients with no evidence of disease after complete resection might therefore benefit from adjuvant or pseudo-adjuvant treatment strategies that aim to prolong disease-free survival and potentially overall survival[19]. The clinical evidence that strengthens the integrated systemic therapy with surgery comes from the cytokines experience; however, this integration has not been widely used with targeted therapy yet [9]. While the use of this integration between surgery and targeted therapy is promising, a correct selection of potential patients should be performed in order to reduce the surgical risks. Further research is necessary o confirm this consolidative treatment in RCC[9].

Nevertheless, some drugs have been used to RCC target therapy. The understanding of the molecular mechanisms involved in carcinogenesis and progression has led to the development of several molecular targeted therapies including VEGF/VEGFR[58]. Cytokines like VEGF and PDGF and associated signal pathways are therapy targets in RCC[5] treatment. Some phase II trials have been addressing the role of trastuzumab (Genetech, San Francisco, CA, USA), an anti-HER2 monoclonal antibody, and bevacizumab, an anti-VEGF monoclonal antibody[25]. Kinase inhibitors, like, Sunitinib and sorafenib, have been tested in phase II and III trials, with excellent clinical results in patients with cytokine refractory disease. Panitumumab (Amgen, Thousand Oaks, CA, USA), antibody of EGFR, and gefitinib (AstraZeneca, Cambridge, UK) and erlotinib (Genetech, San Francisco, CA, USA), inhibitors of EGFR tyrosine kinase were widely assessed[25]. Selective mTOR inhibitors such as temsirolimus exhibited excellent results in a phase III clinical trial[59]. Other agents whose targets are the HIF-1α and CAIX, as well as the anti-CAIX monoclonal radiolabeled antibodies are under development[21].

Before targeted therapies development, cytokines such as IL-2 and interferon-alpha (IFN-α) were extensively used in the mRCC treatment. IFN-α and interleukin-2 (IL-2) provide complete or partial response in 10-15% of the RCC patients. Immunotherapy frequently requires extremely high concentrations and is also associated with various nephrotoxicity[20]. Still, the utilization of IL-2 or IFN-α immunotherapy is restricted to patients with ccRCC in good status[38]. Because of low effectiveness and significant toxicity, cytokines have been used with greater caution and in fewer cases, in high doses with hepatic and bone metastases patients[57]. According to the National Cancer Institute, the disease recurrence after cytokines treatment occurred in all patients who had partial response, while 83% with complete response did not present the disease during follow-up[57].

Other procedures such as allogenic stem cell transplantation, dendritic cell vaccines or biological agents such as tumor infiltrating lymphocytes or lymphokine-activated killer cells have not shown promising results[20]. One promising molecule is the transcription factor nuclear factor kappa B (NF-kB). Although the oncogenic role of NF-kBis still little documented with respect to use in RCC, NF-kB seems to be an attractive target[20]. The tumor necrosis factor α (TNFα) induces the NF-κB activation in RCC cells, which in turn binds to the Rictor gene promoter region. Rictor promotes the cell migration and invasion, probably through the Akt activation[60].

Drugs development that stimulates immune function against tumor cells is now one of the major foci of treatments development against several types of cancers. All invaders express certain markers on their outer membrane, these being recognized by the immune system that induces the T cells production, which attack these invaders. However, tumor cells do not express those markers, in addition to having proteins that inhibit the T cell attack. The spontaneous mutations immune recognition present in tumor cells is inefficient[61]. If the tumors were to express these T cell activator markers, this would induce immunity agsyainst tumor cells. Interferon, for example, stimulates the gene that is already present in the tumor to express this protein, as well as other agents that directly modulate cancer immunity such as cytokines, check points inhibitors, vaccines, adoptive cellular therapy, that have become part of RCC patients' treatment. The chemother-

apeutic agents' association choice with complementary mechanisms of action has fundamental importance in cancer patients' treatment. The immune system stimulus associated with agents that remove co-inhibition, and promote co-stimulation, is required for providing the micro-tumor environment for immunological action[62].

Some drugs indicated for other types of cancer have been used in metastatic renal cancer, such as nivolumab (Bristol-Myers Squibb, New York, NY, USA), an immunoglobulin IgG 4 monoclonal antibody, which binds to Programmed Death 1 receptor (PD-1), expressed in activated T cells, potentiating the immune response against tumor cells. In the InMotion150 phase II trial, which aims to stimulate anti-tumor immunity by combining VEGF blocking and Programmed Death Ligand 1 (PD-L1) in patients with locally advanced or metastatic renal cell carcinoma, it has shown promising results[63]. Although VEGF inhibition improves outcomes in mRCC, most patients develop resistance usually within one year. The use of these two agents, according to the authors, stimulated antitumor activity in patients with mRCC. The safety of combined treatment was consistent with the safety profiles of each individual treatment, with the clinical efficacy of atezolizumab (Genetech, San Francisco, CA, USA) plus bevacizumab being evaluated in phase III of the InMotion151 trial[63].

The innate and adaptive arms of the immune system work in a coordinated fashion to generate an effective immune response against tumor cells. Tumor cells, in general, develop adaptive mechanisms capable of creating an immunosuppressive microenvironment, protecting themselves from the immune system action[64]. The PD-1/PD-L1 interaction inhibits T-cell activation, as well as the cytotoxic T lymphocyte-associated protein 4 (CTLA-4), so there is an increase in PD-L1 synthesis by the tumors and the surrounding cells, in response to T cell activity. Inhibitory agents of this pathway showed wide activity against different types of tumors[65]. Strategies for the next generation anti-CTLA-4 antibodies include non-fucosylated ipilimumab (Eisai, Tokyo, Japan) to increase activity through increased binding of FcγR and an anti-CTLA-4 version to improve drug safety[66].

A study with bladder cancer patients, PD-L1 was considered a biomarker of atezolizumab antitumor response. In lung cancer, the phase III OAK study demonstrated that PD-L1 improved patients' response to atezolizumab treatment, a PD-1 / PD-L1 interaction blocker. Blocking this interaction using agents such as atezolizumab may facilitate the T cells initiation and expansion by blocking or reversing their exhaustion[65]. The PD-1/PD-L1 axis responded to old questions of cancer immunology, proving to be a mechanism that promotes local immune suppression within the micro tumor environment in a lot of solid tumors. Segmenting this pathway therapy has led to lasting remissions in a subset of patients in a variety of malignant tumors[67]. Knowledge of this important mechanism in antitumor immunity has established the basis for the development of a number of immunotherapeutic modalities, including cancer vaccines, transfer of adoptive T cells and monoclonal immune-modulating antibodies[67].

PD-1/PD-L1 inhibitors pharmacologically prevent the PD-1 / PD-L1 interaction, thus facilitating a positive immune response against the tumor, however their activity depends on the generation of T cells capable of recognizing the tumor[68]. However, not all tumors that express PD-L1 respond to PD-1 / PD-L1 inhibitors. On the other hand, it has been observed that PD-L1-negative tumors may respond to these agents[69]. An immunological control point inhibitor combination with a targeted antiangiogenic agent, a complementary action mechanism, might profit from the RCC treatment, and it may also represent a near future of this pathology management. Avelumab (Pfizer, New York, NY, USA) is a fully human anti-PD-L1 IgG1 antibody with clinical activity in different tumor types. JAVELIN Renal 100 trial is a Phase Ib study that evaluates the safety and clinical activity of avelumab more axitinib (Pfizer, New York, NY, USA), a VEGF receptor inhibitor, approved for the second line RCC treatment. The safety profile of the avelumab plus axitinib combination seems compatible with those of monotherapy, and an early antitumor activity was observed. This follow-up is still underway in a clinical trial NCT02493751[70].

According to recent update presented in the AACR 2017, the patients treatment with an immune checkpoint inhibitor in different types of cancer has showed very long results, mainly when the targets are the immune checkpoint proteins PD1 and PDL1. With the use of nivolumab, an anti-PD1, the responses lasted for several years. In a phase I clinical trial, CA209-003, patients with Advanced Non-Small-Cell Lung Cancer had promising clinical results[58]. Data from a phase I clinical study showed that patients with metastat-

ic triple-negative breast cancer experienced positive responses to the anti-PDL1 inhibitor atezolizumab, with significantly greater overall survival compared to those patients who did not respond to treatment[71].

Results from the Phase III clinical trial of CheckMate 067 showed that patients with advanced melanoma who received a combination of nivolumab and the anti-CTLA4 immune control point inhibitor, ipilimumab, improved overall survival compared to those receiving ipilimumab alone[72]. These data suggest that the combination of nivolumab plus ipilimumab offers superior survival results compared to ipilimumab alone[73]. However, the combination also results in a higher rate of serious adverse events than nivolumab or ipilimumab alone.

Responses in patients with advanced Merkel cell carcinoma treated with avelumab were durable. Data from a phase II clinical trial, JAVELIN Merkel 200, showed that patients with advanced Merkel cell carcinoma, an aggressive type of skin cancer, responded to the anti-PDL1 avelumab immunotherapeutic, presenting durable responses[74]. Although the most recent data from these clinical trials attest to the durability of immune control point inhibitor responses, it is important to note that only a fraction of patients in these trials have responded to these therapies: Some patients experienced serious side effects and some developed resistance to treatment. Specifically, patients who used nivolumab instead of everolimus in the treatment of advanced renal cell carcinoma presented the lowest adverse reactions and thus a better quality of life on the other hand, as it can be demonstrated by the CheckMate 025 study[75].

Other CheckMate studies that demonstrated important long-lasting results were the 142, nivolumab in the treatment of patients with metastatic colorectal cancer[76]; the 012 with nivolumab plus ipilimumab in the treatment for advanced non-small-cell lung cancer[73]; the 141 with nivolumab versus standard, single-agent therapy in the treatment of metastatic squamous cell carcinoma of the head and neck[77]; the 032 with nivolumab monotherapy in metastatic urothelial carcinoma[78]; the 64 with nivolumab and ipilimumab in advanced melanoma[79]; the 037 nivolumab versus chemotherapy in patients with advanced melanoma[80]; and still 69 with nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma[81]. All these studies have shown promising results such as nivolumab, an immune checkpoint inhibitor.

Initially used in the medullary thyroid cancer patient's treatment, the Cabozantinib (Exelixis, San Francisco, CA, USA) is a small molecule tyrosine kinase inhibitor (TKI) recently approved for the metastatic renal cell carcinoma treatment by FDA. Cabozantinib also inhibits MET, VEGFR type 2, AXL and other tyrosine kinases such as RET, KIT and FLT3. MET is involved in the survival, invasion, angiogenesis and metastasis of cancer, whereas AXL is a metastasis mediator through crosstalk and resistance to TKIs[82]. In METEOR, a randomized phase 3 trial with advanced renal cell carcinoma patients, comparing the cabozantinib safety and efficacy versus everolimus, an mTOR inhibitor, showed that cabozantinib increased overall survival, delayed disease progression, and improved the objective response of patients to everolimu[82]. Likewise, in the Alliance A031203 CABOSUN Trial, a randomized study of patients with metastatic RCC treated with sunitinib or cabozantinib, also showed a better disease-free survival when compared to sunitinib[83]. Another study with RCC pediatric patients treated with cabozantinib showed a significant disease regression and tolerable adverse effects[84]. Finally, a meta-analysis compared the short-term efficacy of single drugs therapies in RCC treatment. The study shows that the partial response, the overall response rate, the complete response, stable disease, progressive disease, as well as the disease control rate, in patients treated with cabozantinib had the best short-term efficacy, being higher to sorafenib, sunitinib, while everolimus had the worst short-term efficacy[85].

Immunotherapy is the fastest growing area on oncology, offering an effective alternative treatment and remission of previously untreatable tumors. The immune structure determined by the density, composition, functional status and organization of the leukocyte infiltrate in the tumor can provide relevant prognostic information and a response to treatment prediction, allowing an individual approach to each patient. The Immunoscore potential, which is a histology-based assay to assess the immunoreactivity surrounding tumors, providing knowledge of pre-existing anti-tumor immunity may guide the selection of efficient and personalized immunotherapy for patients[86].

The potential prognosis of CD8+ and PD-L1 and tumor cell densities in determining the response to anti-PD-L1 therapy is another tool that has been used in the treatment of different cancers. One study used an automated cell density

imaging, showing that patients with high CD8+ and PD-L1 cell density in non-small cell lung cancer presented better responses with durvalumab (AstraZeneca, Cambridge, UK) treatment, as well as longer survival without relapses[87].

The immunomodulatory role of the intestinal microbiota on cancer therapy is also apparent with immune control point blocking therapies, such as the blockade of CTLA-4 by ipilimumab. Absorption of distinct bacterial species or bacterial products by dendritic cell can significantly improve the processing and presentation of dendritic cell antigen[88]. These results suggest that intestinal microbiota modulation may represent a new therapeutic strategy to increase the antitumor efficacy of anticancer compounds. Other studies demonstrating that elevated body temperature or use of β-blockers improves the efficacy of anti-PD-1 therapy in tumor-bearing rats compared to any monotherapy ($p<0.001$), associated with an increase in T CD8+ cell numbers[89]; as well as data suggest that the patient's lifestyle interventions can improve the ability to respond to emerging immunotherapies[90].

Lungs and bones metastases are the most common in mRCC. The strongest metastasis predictors are disease-specific factors, such as clinical T stage, and Fuhrman's higher grade. In pRCC and chRCC localized disease is the most common, whereas for ccRCC the most common is the patient presenting at the moment of the diagnosis, advanced or metastatic disease. For cancer-specific mortality, the presence of brain and liver metastases is associated with poor prognosis than lung or bone metastases[91].

Targeted agents use has shown lasting efficacy in the mRCC treatment. FDA approved agents are multidirectional tyrosine kinase inhibitors (TKIs) such as sunitinib, sorafenib, axitinib, pazopanib, cabozantinib and lenvatinib (Eisai, Tokyo, Japan); the anti-VEGF monoclonal antibody such as bevacizumab; the rapamycin (mTOR) inhibitors: like everolimus and temsirolimus, and the programmed immune control point inhibitor mort-1 (PD-1), nivolumab[92,93]. Sorafenib is a treatment option in metastatic RCC, although a high incidence of adverse reactions is observed[94].

The use of target therapy has facilitated surgery in patients with locally advanced or metastatic RCC. The association between TKI and surgery seems to have no contraindications[95]. The use of high dose of IL-2 plus radiotherapy has led to a significant response in patients with mRCC, where it has been shown that over 36 months after the metastatic disease diagnosis, the patient remained in remission[96]. In Table II, the main Therapeutic Targets Agents to RCC approved by FDA are shown[97-101].

Discussion

In renal cell carcinoma, the genetic alterations are quite important in the tumorigenesis processes and these mechanisms elucidation has been providing a greater knowledge on cellular pathways in cancer, and thus providing new therapeutic targets. Patients with VHL disease, for example, establish important genetic alterations involving the 3p chromosome that are lost in 80-98% of patients with sporadic ccRCC. Without a doubt, RCC is a pathology highly associated with genetic alterations that trigger its development.

With advance of technology, we have a better idea of the gene changes responsible for some forms of RCC. To choose the best treatment option, it is important to consider variables related to the patient, such as comorbidities, histological tumor type, clinical, genetic and laboratory data, mainly prognostic risk factors, as well as used drugs toxicity degree. Several clinical trials are underway to establish the best and most effective treatments for different types of RCC. Immunological therapies have been taking place within the various therapeutic regimens, since chemotherapy has not been shown to be effective in advanced and / or metastatic kidney cancers. For cancers that cannot be removed with surgery or small tumors, immunotherapy has been the first choice. Other clinical trials have been evaluating whether the combination of medications already in use, either among them or with other treatment types, may be better than using them isolatedly. Neoadjuvant and adjuvant therapies, administered before and after surgery, have also been studied to increase cure rates, and/or to shrink tumors prior to surgery, thus maintaining renal function preserved.

Other studies have been moving through with promising results in improving immunotumoral activity, such as CheckMate 032 phase I and II multicenter trial, which uses ipilimumab combined with nivolumab, open for patients with advanced or metastatic urothelial cancer, and it showed very encouraging preliminary results[78]. Immunotherapies have been showing encouraging prognoses in the cancer treatment. Different types of vaccines that stimulate the body's im-

Table II. Therapeutic agents to RCC and targets approved by FDA,

Drug	Target	Indication	Reference
Axitinib	Tyrosine kinase inhibitors second generation VEGFR-1,-2,-3	Advanced RCC after failure of one prior systemic therapy, after antiangiogenic or cytokine therapy (Category 1, 2A)	97, 98, 99
Bevacizumab	Tyrosine kinase inhibitors; monoclonal antibody neutralizes VEGF-A circulating	Metastatic RCC (stage IV) after anti-angiogenic or cytokine therapy (Category 1, 2A, 2B)	97, 98, 99
Cabozantinib	Tyrosine kinase inhibitors including VEGF-receptors; MET; AXL; FGFR	Advanced RCC after antiangiogenic therapy (Category 1)	97, 98
Everolimus	Tyrosine kinase inhibitors of mTOR	Advanced RCC after failure of treatment with Sunitinib or Sorafenib, after antiangiogenic therapy (Category 1)	97, 99
Interleukin-2 (IFN-α)	Imunotherapy result in effector T-cell exhaustion	Metastatic RCC who had undergone nephrectomy (Category 2B)	97, 99, 100
Lenvatinib	Tyrosine kinase inhibitors including FGFR	Advanced RCC after antiangiogenic therapy	97, 101
Nivolumab	Blocks interaction between PD-1 (T cells) and ligands (immune and tumor cells)	Metastatic RCC, who have received a certain type of prior therapy, after antiangiogenic therapy (Category 1)	97, 100
Pazopanib	Tyrosine kinase inhibitors first generation including PDGFR- α,−β; VEGFR-1,-2,-3; c-KIT	Advanced RCC (stage IV) after anti-angiogenic or cytokine therapy (Category 1, 2A)	99-101
Sorafenib	Tyrosine kinase inhibitors first generation including PDGFR-α; VEGFR-1,-2,-3; c-KIT; FLT-3; RET	Advanced RCC (stage IV) after anti-angiogenic or cytokine therapy (Category 1, 2A, 2B)	97, 98
Sunitinib	Tyrosine kinase inhibitors first generation including PDGFR-α,−β; VEGFR-1,-2,-3; c-KIT; FLT-3; CSF-1R; RET	Metastatic RCC based on partial response rates and response duration, after anti-angiogenic or cytokine therapy (Category 1, 2A)	97, 98, 99
Temsirolimus	Tyrosine kinase inhibitors of mTOR	Advanced RCC, after antiangiogenic or cytokine therapy (Category 1, 2A, 2B)	97, 99

mune response against kidney cancer cells have been tested in clinical trials. One possible advantage of this treatment type is that fewer side effects occur. Among the ways to create a vaccine is to use the patient's own cancer cells (removed during surgery, for example), being altered in the laboratory to make them more likely to stimulate an immune response and reintroduced into the patient[102].

Individualized mutant vaccines implement an RNA-based approach to mobilize immunity against a spectrum of cancer mutations, already applied in melanoma. Individual mutations have been identified, neoepitopes computational prediction have been made, as the design and manufacture of a single vaccine for each patient. Through vaccine-induced T cell infiltration, the specific killing of autologous tumor cells by neoepitopes occurs, personalized cancer vaccines may help prevent melanoma, as demonstrated in Phase I Clinical Trials[61]. The findings boosted an emerging field that uses unique neoantigens from each patient's cancer so that the immune system kills the cancer cells[103].

Some viruses can be altered to carry a gene for a marker protein to be recognized by the immune system. Phase I and II data on Coxsackievirus A21 (CVA21), a new intra cellular adhesion molecule-1 targeted oncolytic virus in patients with non-invasive muscle bladder cancer, which had a characteristic positive regulation of Intercellular Adhesion Molecule 1 expression, received CVA21 neoadjuvant or low dose of mitomycin C plus CVA21 prior to surgical removal. Intra vesicular CVA21 alone or in combination, demonstrated clinical activity, leading tumor cells to apoptosis probably due to the increase of immune cells in the tumor infiltrate. Viral replication, superficial inflammation and vi-

rus-induced hemorrhage were observed. Gene expression assays illustrate generalized increases in interferon-induced genes, and urinalysis indicated that 69% of the patients had elevated levels of high-mobility group protein 1, an important inflammation mediator[104].

Renal cancer management will evolve at an accelerated pace over the next few years, and patients who combine appropriate therapeutic regimens will likely present increasingly encouraging prognoses. Immunological monitoring, use of drugs that reduce immune system action tumor tolerance, relevant predictive biomarkers validation, use of the genome in clinical trials, are strategies that have been used for the patient's benefit, have certainly been transforming the management of RCC patients or even other types of cancer. Therapeutic strategies should be customized, including different immunotherapeutic drugs, in combination with chemotherapeutic agents, determining when diagnosis should be used in each case[105]. In addition, the emergence of new technologies such as the neoantigenic functional expansion associated with specific T cell mutation could help define antigenic peptides to formulate custom vaccines[106]. Understanding the drugs action mechanisms, to obtain complementary associations in the fight against cancer, developing combined therapies and reducing adverse effects are the currently efforts being made to boost advances in cancer treatment.

Conclusions

Despite the unprecedented increase in the understanding of molecular mechanisms and development of numerous chemo and molecular regimens for RCC, the overall 5-year survival rate rarely exceeds 10%[11]. However, the searches for new molecular targets for RCC with some clinical importance are still far from clinical use. Patients with metastatic RCC have, with a few exceptions, minimal to no curative options[47]. The search of new therapeutic agents for advanced RCC is an urgent priority. Therefore, new discoveries in our understanding of the molecular carcinogenesis mechanisms and RCC progression have been fundamentally researched.

In summary, the most commonly used therapeutic regimens in mRCC are sorafenib and temsirolimus as a first-line option; the combination of Cytokine therapy with interferon (IFN)-α with bevacizumab and sunitinib are also first-line treatments for mRCC. Cabozantinib, and nivolumab are recommended as a second-line therapy option in mRCC. Pazopanib for the second line, and everolimus and axitinib are among the third line of treatment. Failing therapy with VEGF and mTOR, dovitinib (Novartis, Basel, Switzerland) showed activity in the third line[26].

Immunotherapy has also been a mRCC treatment option. VEGF and mTOR agents have been the most effective strategy today, but advances in immunotherapy have contributed to the mRCC treatment. With the recent update of the human atlas on the immune tumor microenvironment in RCC, new potential targets for immunotherapy with a focus on macrophages arose. In addition to the isolated use, some combinations have been tested in mRCC, such as CTLA-4 agents with anti-PD-1; TKI with anti-PD-1, or bevacizumab and anti-PD-1 for example[80].

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Authors' Contributions

GDP, and JYP conceived and designed the study; HNL, PES, WS, SD, and AP reviewed and added Information to the text. All authors read and approved the final manuscript.

Informed Consent

Informed consent was not used in this research because it did not involve humans directly, because it was a review. The Ethics Committee approval of the included studies was observed.

Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

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