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Current perspectives on systemic therapy for metastatic non-clear cell renal cell carcinoma

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Abstract

The improvements in the knowledge of the underlying biology of renal cell carcinoma (RCC) has led to consider this disease as a group of different entities characterized by their pathological phenotype, and the particular features exhibited in their microenvironment. Non-clear cell RCC (nccRCC) represents a heterogeneous group of kidney cancers showing different genetic, histologic, and morphological characteristics that in turn lead to diverse biologic behaviors.

Since nccRCCs are infrequent, they are commonly scarcely represented or excluded from most randomized controlled trials, making data on the efficacy of current treatment options still limited, and the optimal systemic therapeutic schedule for the treatment of advanced stages yet to be defined.

This review summarizes the available literature regarding the salient morphogenetic features encountered among the different nccRCC subtypes, and updates the evidence provided by the current studies reporting on the efficacy of targeted therapy in this kind of tumors.

Introduction

The management of renal cell carcinoma (RCC) has undergone a dramatic change in the last three decades. An enhanced understanding of its underlying biology has allowed a partial identification of unique molecular alterations and signalling pathways that modulate the proliferation and growth development of the different RCC variants. Therefore, RCC is no longer considered a single disease, but a group of different entities that can be characterized not only by their pathological phenotype, but for the particular features exhibited in the microenvironment of each of the different tumor variants. In this way, the evolving landscape of systemic therapy using synergic combinations aimed to target different angiogenic and immune microenvironment profiles, has resulted in an improved overall survival (OS) of those patients harboring a clear-cell metastatic RCC (mRCC)[1].

Non-clear cell renal cell carcinoma (nccRCC) represents a heterogeneous group of kidney cancers showing different genetic, histologic, and morphological characteristics that in turn lead to diverse biologic behaviors. Today, most authors agree to recognize nccRCC as a disease entity completely separated from the clear-cell variant[2]. Since nccRCC are infrequent (25-20% of all RCC cases), they are commonly scarcely represented and excluded from most randomized controlled trials (RCTs), making data on the efficacy of targeted therapy in terms of objective response rate (ORR) and progression-free survival (PFS) still limited, and thus the optimal systemic therapeutic schedule for the treatment of advanced stages of the disease yet to be defined. Uncertanties regarding the adequate management of sarcomatoid tumors (a dedifferentiated form potentially occurring from almost all histologic subtypes of RCC) still also exist[3].

This review summarizes the available literature regarding the salient morphogenetic features encountered among the different nccRCC subtypes, and updates the evidence provided by the current studies reporting on the efficacy of targeted therapy in this kind of tumors.

Pathologic subtypes of nccRCC

According to the World Health Organization 2016 Classification, the nccRCC group is composed of different histologic subtypes including papillary (10-15%), chromophobe (5%), collecting duct (Bellini) (1%), medullary (1%), and MiT family translocation (1%) RCCs. Furthermore, new entities of nccRCC with yet undefined frequencies have been added to this classification, thus completing this group (succinate dehydrogenase B-deficient RCC, and hereditary leiomyomatosis and RCC syndrome-associated RCC with fumarate hydratase (FH) deficiency.

Papillary Renal Cell Carcinoma

Papillary tumors have their origin at the proximal convoluted tubule[4]. Although papillary architecture represents the most frequent histologic pattern, tu-

Table 1. Subtypes of nccRCCs and their commonly detected molecular alterations.

nccRCC variant	Frequency (%)	Genetic alterations
Papillary RCC (type I and II)	10-15%	+3q, +7, +8, +12, +16, +17, +20, -Y SLC5A3, NF2, PNKD, CPQ, LRP2, CHD3, SLC9A3R1, SETD2, CRTC1 Type I: MET Type II: fumarate hydratase, methylator phenotype, p16/CDNK2a
Chromophobe RCC	5%	Chromosome 1,2,6,10,13,17, and 21 hypodiploidy Up-regulation KIT Breakpoints TERT TP53, PTEN, FAAH2, PDHB, PDXDC1, and ZNF765 17p11 (Birt-Hogg-Dubé Syndrome)
Collecting duct RCC/ Bellini duct RCC	1%	-1p,-8p,-16p,+13q, NF2, SETD2
Medullary RCC	1%	Mutations ALK, loss of SMARCB1, amplification ABL/BCR
MiT family translocation RCC	1%	Fusion genes TFE3 or TFEB MiTF, TGF-beta1, PI3K, BIRC7
Succinate dehydrogenase-B deficient RCC	<1%	Double-hit inactivation of SDH genes
Hereditary leiomyomatosis and RCC syndrome- associated fumarate hydratase deficiency	<1%	Fumarate hydratase
Tubulocystic RCC	<1%	+17p, +17q
Acquired cystic kidney disease associated RCC	<1%	+3, +7, +17, -Y
Unclassified RCC	<1%	unknown
Sarcomatoid differentiation	15-20% (of all RCCs)	TP53, VHL, CDKN2a, NF2, PBRM1, SETD2; PTEN, ARID1A, BAP1

Abbreviations: Renal cell carcinoma (RCC); Sodium/myo-inositol cotransporter 5A3 gene (SLC5A3); Neurofibromin 2 gene (NF2); Paroxysmal nonkinesiogenic dyskinesia gene (PNKD); Carboxypeptidase Q gene (CPQ); Low density lipoprotein-related protein 2 gene (LRP2); Chromodomain Helicase DNA Binding Protein 3 gene (CHD3); Sodium/myo-inositol cotransporter 9A3 receptor 1 gene (SLC9A3R1); SET domain containing 2 gene (SETD2); CREB Regulated Transcription Coactivator 1 gene (CRTC1); N-methyl-N'-nitroso-guanidine human osteosarcoma transforming gene (MET); Cyclin-dependent kinase inhibitor 2A gene (CDNK2A); Cluster of differentiation 117 gene (KIT); Telomerase reverse transcriptase gene (TERT); Breast cancer 1 gene (BRCA1); Tumor protein 53 gene (TP53); Phosphatase And Tensin Homolog gene (PTEN); Fatty Acid Amide Hydrolase 2 gene (FAAH2); Pyruvate Dehydrogenase E1 Subunit Beta gene (PDHB); Pyridoxal Dependent Decarboxylase Domain Containing 1 gene (PDXDC1); Neighboring zinc finger protein 765 gene (ZNF765); Anaplastic lymphoma kinase (ALK); SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily B, Member 1 (SMARCB1); Abelson Murine Leukemia gene (ABL); Succinate dehydrogenase gene (SDH); Breakpoint Cluster Region gene (BCR); Fusion between ABL and BCR genes (ABL/BCR); Transcription Factor For Immunoglobulin Heavy-chain Enhancer 3 gene (TFE3); Transcription Factor EB (TFEB); Microphtalmia associated transcription factor (MiTF); Transforming Growth Factor gene (TGF); Phosphatidylinositol 3-kinases gene (PI3K); Baculoviral IAP Repeat Containing 7 (BIRC7); Von Hipple Lindau gene (VHL); BRCA1 Associated Protein 1 (BAP1). "+": insertion mutation; "-": deletion mutation.

bular and solid growth patterns may also be present. The tumor papillae contain a delicate fibrovascular core accompanied by certain amount of edema or hyalinized connective tissue. Depending on their genetic characteristics, two different types of papillary RCC can be distinguished: type I (better prognosis) and II (worse prognosis)[5]. Although several immunohistochemical markers have been proposed to date to differentiate between both types, but none of them has been validated for use in routine practice. Furthermore, a clear difference between both types may be difficult to set, since a mixture of both types is frequently seen in the same case.

Genetically, both types are characterized by extra copies of chromosomes +3q, +7,+8,+12, +16, +17, and +20. When these alterations are present, they strongly suggest a papillary etiology, although the papillary histologic pattern would be not predominant.

Type-1 papillary RCC is genetically characterized by different alterations in the MET gene that suggest a crucial role of these alterations in its pathophysiology, and include somatic (seen in up to 81% of the sporadic forms) and germline (infrequent) mutations of MET gene, or an altered chromosome 7 carrying the MET gene. Patients with type-1 papillary RCC are commonly diagnosed at earlier stages and thus, as a general rule, exhibit a clinically better prognosis after treatment[6,7].

Type-2 papillary RCCs are nowadays thought to correspond not to a single disease, but rather to a group of different diseases showing unique characteristics from the genetic standpoint. As such, at least three different genetic clusters have been already identified. Mutations in the gene encoding fumarate hydratase (FH) are frequently seen in these tumor variants, including germline mutations (some of them shared with the complex hereditary leiomyomatosis and RCC) that have been associated with poor prognosis (FH deficency). The increased methylation of different genes (methylator phenotype), and alterations affecting p16/CDNK2a represent other genetically altered variants confering poorer prognosis, and thus inferior survival rates to this subgroup[8].

Chromophobe Renal Cell Carcinoma

This pathologic subtype of nccRCC develops from the intercalated cells of the collecting duct system[9]. Its growth pattern is solid, but tubular architecture can be also present. Ocasionally, focal calcifications and broad fibrotic septa (long linear vessels) are encountered. Genetically, it is characterized by hypodiploidy in a number of chromosomes including 1, 2, 6, 10, 13, 17, or 21 from the genetic point of view[10]. In addition, mutations in the p53 gene, upregulation (overexpresssion/amplification) of the proto-oncogene KIT (not induced by mutations but by multiple copies of the wild type-KIT gene), and breakpoints in the gene of the telomerase reverse transcriptase (TERT) have been detected in this subgroup (mitochondrial DNA alterations are more common in chromophobe RCC than in clear cell RCC), thus increasing the landscape for reseach regarding new targeted therapeutic strategies to fight against these tumors[9-13]. Recently, TP53, PTEN, FAAH2, PDHB, PDXDC1, and ZNF765 were found to be significantly mutated in chromophobe RCC specimens[14].

Most chromophobe RCCs are sporadic. However, renal tumors with similar morphology but distinct genetic features can be associated with Birt-Hogg-Dubé (BHD) syndrome. The BHD gene is located on chromosome 17p11 and encodes a potential tumor suppressor protein called folliculin[15]. Nevertheless, chromophobe RCC patients commonly exhibit better prognosis and longer overall survival (OS) rates than clear cell RCCs[16].

Bellini duct carcinoma

The collecting duct carcinoma is an infrequent pathologic subtype that originates from the collecting duct cells and is delineated by loss of heterozygosity (deletions) of chromosomes -1p, -8p, and -16p, amplification of +13q, and mutations of NF2 (29%) and SETD2 (24%). These tumors present an aggresive clinical course commonly characterized by the presence of hematuria[17-20].

Medullary carcinoma

Medullary carcinoma affects typically young patients with sickle cell disease or asymptomatic carriers (heterozygous) of the sickle cell allele, and it is thought to arise at the renal pelvic-mucosal interface, growing rapidly within the renal pelvis to invade shortly after the vascular and lymphatic structures. This characteristic growth pattern translates in a genetic overlap with proximal urothelial cancer. However, due to its infrequency it is difficult to draw a single mutational map, that should include (among others) mutations in the ALK gene, loss of SMARCB1 (INI1), and more rarely amplification of BCR and ABL genes (a possible therapeutic target for a minority of these types of tumor)[21,22].

MiT family translocation RCC

Xp11.2 RCC represents an underdiagnosed subtype of RCC. It belongs to the family of microphthalmia transcription factor (MiTF)-associated tumors, and are genetically characterized by translocations involving Xp11.2, which results in a gene rearrangement involving the TFE3 gene[23]. Genome-wide analysis (RNA/exome sequencing) has recently identified other three novel MiTF/TFE partners involved in RNA splicing, expanding the spectrum of translocations associated with this disease[24]. Elevations in baculoviral IAP repeat-containing protein 7 (BIRC7) expression were observed in the majority of Xp11.2 RCC, which may be useful in the diagnosis of all MiTF family members[25].

Sarcomatoid Tumors

Sarcomatoid RCC (sRCC) originates from the epithelial-mesenchymal transition (EMT) containing both epitelial (carcinoma) and mesenchymal (sarcomatoid) features (spindle cells, high cellularity, and cellular atypia), distinct from primary sarcoma, and probably derived from the same progenitor cell via clonal divergence during tumor progression[26,27]. It is currently not considered a distinct morphogenetic subtype, affecting almost every pathological subtype, and conferring them poorer clinical outcomes even when a small component is present[28]. Genomic profiling has shown identical mutational profiles in both cellular components, with TP53 (42%), VHL (35%), CDKN2a (27%), and NF2 (19%) being the most frequently altered genes[29]. Fewer deletions at 3p21-25, a lower rate of two-hit loss of VHL and PBRM1, more mutations in TP53, PTEN, and RELN, and mutations in known cancer drivers, such as AT-rich interaction domain 1A (ARID1A) and BRCA1 associated protein 1 (BAP1), have been frequently identified in sarcomatoid patterns, thus implicating that specific genes are involved in the sarcomatoid process, leading to unique genetic alterations. Interestingly, induction of EMT may upregulate the expression of PD-L1 and other targetable immune checkpoint molecules. sRCC has been shown to express PD-1/PD-L1 at a much higher level than RCC without sarcomatoid elements, suggesting a biologic distinctiveness of sRCC at the level of immune markers with clear cell and other nccRCC specimens, and making the blockade of the PD-1/PD-L1 axis an attractive therapeutic approach in EMT-derived tumors[31].

Systemic therapy in nccRCC

The treatment landscape for nccRCC has been a spectator of a dramatic change in the last 20 years. In the early 2000s, the tratment of advanced stages of this group of diseases was limited to cytokines (interferon and interleukine-2) in monotherapy or their combination. A wide variety of rather frequent adverse side effects, and marginal therapeutic benefit was obtained from this early experience. However, this strategy paved the way for the further use of tyrosine kinase inhibitors (TKIs), and the more recently incorporated immune checkpoint inhibitors (ICIs) (Table 2).

Vascular Endotelial Growth Factor (VEGF) Inhibition

Sorafenib and sunitib, two VEGF inhibitors were approved by the Food and Drug Administration (FDA) on the basis of the positive results obtained in the treatment of metastatic clear cell variant of RCC compared to placebo and interferon-alpha, respectively. Once available for use, the retrospective analysis of those cases treated in base of medical prescriptions or as part of extended access programs showed durable (8-12 months) partial responses with sunitinib (n=2/12 patients; PFS 7.6 months) for papillary RCCs regardless the presence of clinical prognostic factors, and sunitinib or sorafenib (n=3/12 partial response; PFS 10.6 months; ORR 25%) for chromophobe RCCs[32]. Further prospective phase-II studies have asessed sunitinib in patients harboring a nccRCC. Tannir et al[33] noted that only 2 patients with chromophobe mRCC showed a partial response lasting less than 3 months to the drug. The SUPAP trial reported partial responses with PFS of 6.6 and 5.5 months in a total of 13% and 11% of patients with type-I and type-II papillary RCCs, respectively[34].

More recently, three additional trials have evaluated the efficacy of sunitinib *vs.* everolimus (mTOR inhibitor) in nccRCC patients: ASPEN, ESPN, and RECORD-3. The ASPEN trial showed a beneficial effect of sunitinib in PFS (8.3 *vs.* 5.6 months) and a comparable median OS (16.2 *vs.* 14.9 months), particularly in those patients exhibiting a good/intermediate risk according to the Memorial Sloan Kettering Cancer Center (MSKCC) criteria (PFS 14 *vs.* 5.7 months in good-risk and 6.5 *vs.* 4.9 months in intermediate-risk patients) (Table 3).

Table 2. Current trials in the systemic treatment of nccRCC.

Study	Intervention	Study type	#pts	Histologic subtypes (%)	Outcomes (months or %)
Dutcher et al[41]	Interferon *vs.* temsirolimus	Prospective	73	• Papillary[75] • Chromophobe[15] • Collecting duct[6] • Unclassified[4]	• OS 4.3 vs. 11.6 • PFS 1.8 vs. 7.0
Jonasch et al[66]	Capecitabine, gemcitabine, bevacizumab	Prospective	28	• Sarcomatoid	• OS 5.9 (all) *vs.* 3.9 (sarc) • PFS 10.4 (all) vs. 9 (sarc)
Koh et al[43]	Everolimus	Prospective	49	• Papillary[57] • Chromophobe[14] • Collecting duct[4] • Unclassified[12] • Sarcomatoid[6]	• OS 5.2 • PFS 14
Motzer et al[38]	Everolimus *vs.* sunitinib	Prospective	66	• Papillary[75] • Chromophobe[18] • Unclassified[6]	• OS 5.1 vs. 7.2
Twardowski et al[48]	Tivantinib *vs.* erlotinib+tivantinib	Prospective	50	• Papillary[100]	• OS 2.0 vs. 5.4 • PFS 10.3 vs. 11.3
Buti et al[39]	Pazopanib	Retrospective	37	• Papillary[51] • Chromophobe[24] • MiT translocation family[2] • Unclassified[21]	• OS 15.9 • PFS 17.3
Tannir et al[36]	Everolimus *vs.* sunitinib	Prospective	68	• Papillary[39] • Chromophobe[17] • MiT translocation family • Unclassified • Sarcomatoid	• OS 4.1 vs. 6.1 • PFS 14.9 vs. 16.2
Armstrong et al[35]	Everolimus *vs.* Sunitinib	Prospective	108	• Papillary[70] • Chromophobe[14] • Unclassified[16]	• OS 5.6 vs. 8.3 • PFS 13.2 vs. 31.5
Escudier et al[44]	Everolimus	Prospective	92	• Papillary[100]	• OS 4.1 • PFS 21.4
Matrana et al[40]	Pazopanib	Retrospective	29	• Papillary[24] • Chromophobe[13] • MiT translocation family • Unclassified[17] • PFS 13.6	• OS 4.0
Jay et al[61]	Sunitinib+ gemcitabine	Prospective	72	• Clear cell -high risk • Sarcomatoid	• Not available
McKay et al[67]	PD-1/PD-1-L blockers	Retrospective	43	• Papillary[33] • Chromophobe[23] • MiT translocation family[7] • Unclassified[21] • Sarcomatoid[16] • ORR 19%	
Koshkin et al[49]	Nivolumab	Retrospective	41	• Papillary[39] • Chromophobe[12] • MiT translocation family[4] • Collecting duct[10] • Unclassified[34]	• ORR 20%

Continued

Table 2 ***(continued).*** Current trials in the systemic treatment of nccRCC.

Study	Intervention	Study type	#pts	Histologic subtypes (%)	Outcomes (months or %)
Vogelzang et al[50]	Nivolumab	Prospective	44	• Papillary[54] • Chromophobe[16] • Others[11] • Unclassified[18]	• ORR 13.6%
McDermott et al[51]	Pembrolizumab	Prospective	165	• Papillary[72] • Chromophobe[13] • Unclassified[16]	• ORR 24.8%
Powles et al[52]	Savoltinib+ durvalumab	Prospective	42	• Papillary[100]	• ORR 27%
Gupta et al[53]	Ipilimumab+ nivolumab	Retrospective	13	• Papillary[23] • Chromophobe[23] • MiT translocation family[7] • Medullary[7] • Others[15]	• ORR 17%
Flippot et al[54]	Atezolizumab+ bevacizumab	Prospective	39	Not specified	• ORR 26%

Abbreviations: ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Conversely, high-risk patients showed a significantly better PFS for treatment with everolimus (6.1 *vs.* 4.0 months)[35]. The ESPN trial reported no significant benefit in terms of PFS or median OS for sunitinib. A mild benefit for sunitinib in terms of median OS was exclusively noted for those patients not exhibiting sarcomatoid dedifferentiation in the first-line setting[36,37]. The meta-analysis of the pooled data of both trials documented no significant difference in PFS for both substances (HR 1.3; P=.15), but a trend for superiority of sunitinib, leading to a National Cancer Comprehensive Network (NCCN) recommendation favoring sunitinib over mTOR inhibition in these patients. Finally, the subgroup analysis of RECORD-3 reported comparable PFS rates for sunitinib and everolimus[38].

Current experience with pazopanib in nccRCC is limited to retrospective studies. In 2017, Buti et al[39] reported a median PFS, and OS of 15.9, and 17.3 months for the treatment with pazopanib in those patients with nccRCC included in the single-arm retrospective study so-called PANORAMA. This benefit for pazopanib was further confirmed in another retrospective study in both the first-line and second-line settings[40]. However, the use of pazopanib is not recommended in clinical routine and should be limited to RCTs, given that prospective data or comparative studies are still unavailable.

mTOR Inhibition

To date, many reports have proven a benefit of temsirolimus compared to cytokines (IFN-α) in the treatment of mRCC[44]. The subgroup analysis of the Advanced Renal Cell Carcinoma (ARCC) study showed a comparable median OS for clear-cell RCC (ccRCC) and nccRCC patients receiving temsirolimus[41]. Furthermore, temsirolimus showed a higher objective response rate (ORR) in nccRCC patients. These data resulted in a recommendation from the NCCN for temsirolimus in nccRCC, particularly in the poor-risk group of the Memorial Sloan Kettering Cancer Center (MSKCC) classification (Table 3).

Everolimus has been tested in other three additional studies. The subgroup analysis of the RAD001 Expanded Access Clinical Trial (REACT) demonstrated an ORR of 50.6% and a PFS of 2.8 months for everolimus[42], while another trial reported a benefit for everolimus in terms of median OS (14 months) and PFS (5.2 months) for patients harboring a VEGF-inhibition refractory disease, which resulted especially high in cases of chromophobe RCC[43]. Finally, the RAPTOR trial showed similar results concerning PFS for patients with papillary histology (median OS of 21.4 months)[44].

Table 3. The Memorial Sloan Kettering Cancer Center (MSKCC) criteria for the prognosis of advanced RCC and risk-adjusted category groups.

Stratification System	Criteria	Grades (median overall survival in months)
Memorial Sloan Kettering Cancer Center (MSKCC) stratification system (cytokine era)	• Karnofsky Status performance <80% • Time between diagnosis and starting of systemic treatment < 1 year • Serum hemoglobin level below the lower level of normal • Corrected serum calcium >10 ng/dL • Lactate dehydrogenase level above the upper limit of normal	• Favorable 0 risk factors (20) • Intermediate 1-2 risk factors (10) • Poor >3 risk factors (4)

MET and EGFR Inhibition

Different studies have pursued improved outcomes in the management of extended nccRCC by identifying specific genetic targets for the different histologic subtypes of nccRCC. In this way, The Cancer Genome Atlas (TCGA) research group identified alterations (amplification, duplication, or mutation) of the MET gene or a gain in chromosome 7 (harboring MET gene) in approximately 80% of the papillary type-I tumors included in their study. As a result, different TKIs targeting the MET-related pathway have been further asessed in phase-II trials, including: foretinib, savoltinib, crizotinib, tivantinib, and cabozantinib.

Foretinib, crizotinib, and cabozantinib are multikinase inhibitors targeting MET, and other receptors (foretinib: VEGF, RON, AXL, TIE2; crizotinib: ROS1, ALK; cabozantinib: AXL, VEGF2, RET), while savolitinib is a highly selective MET inhibitor. Different phase-II trials (biomarker-BASED, PAPMET, and CREATE trials among others), have demonstrated better outcomes with the use of these drugs in papillary type-I mRCCs. In fact, cabozantinib is recommended in the front-line therapy for extended nccRCC, even when no phase-III trial outcomes are still available, based in part on the results provided by a retrospective study in which the MET-altered positive cohort exhibited an ORR of 40% (superior to ORR of 27% exhibited by the entire cohort). Conversely, the SAVOIR trial comparing sunitinib *vs.* savoltinib was prematurely closed before meeting the recruitment objectives due probably to discouraging results (unpublished outcomes)[45-47]. The definitive outcomes of the PAPMET trial are still unpublished, but its treatment protocol has been revised recently to remove the crizotinib and savoltinib arms due probably to futile analysis. Further studies combining MET inhibition and ICIs are expected in the next future.

The epidermal growth factor receptor (EGFR) inhibitor erlotinib in monotherapy showed certain benefit in terms of ORR (11%) in papillary RCCs (SWOG 0317). However, a phase-II study evaluating the outcomes of erlotinib *vs.* erlotinib-tivantinib has been sttoped recently after the interim analysis due to lack of efficacy in both treatment arms[48], making erlotinib no longer recommended outside clinical trials.

Immune checkpoint inhibition

Most of the immune checkpoint inhibitors (ICIs) available, gained approval based on the results of different trials that excluded the non-clear cell variants of RCC in their protocol. As such, the available experience with ICIs in the nccRCC setting is mostly limited to retrospectives studies. ORRs of approximately 20% have been reported using anti-PD-1/PD-1L therapy in monotherapy or in combination with anti-CTLA4 or anti-VEGF drugs in papillary, collecting duct, and unclassified tumors[49].

Several prospective trials including the Checkmate 374, KEYNOTE 427, and CALYPSO have evaluated the response to different ICIs or ICI combinations in the treatment of mRCC. All these protocols included a subset of patients harboring a nccRCC. Therefore, although limited by the small simple sizes, some meaningful conclusions from theses studies can be extrapolated. The Checkmate 374 study (nivolumab) included a total of 44 patients with nccRCC. The ORR reported for this cohort was 13.6% at a median follow-up of 11 months. Interestingly, one patient harboring a chromophobe RCC exhibited a complete response. KEYNOTE 427 (pembrolizumab) included in its cohort B a

total of 165 patients with papillary (71%), chromophobe (13%), and unclassified (16%) nccRCCs. At a median follow-up of 11 months, the ORR reported was 25%, which was especially promising for the unclassified variant (specific ORR 35%). The CALYPSO trial (savoltinib+durvalumab) reported a consisting ORR of almost 30% in this regard. Finally, the combinations nivolumab+ipilimimab and atezolizumab+bevacizumab have reported ORRs of 28% and 26% in the treatment of different nccRCC histologic variants[50-58].

Sarcomatoid differentiation

Sarcomatoid differentiation shows a wide variety of genetic alterations. These alterations may represent specific target agents for treatment upon appearance. However, to date no standardized therapy schedule is still available. Therefore, current guidelines lack well-defined recommendations for optimal treatment. Since early reports assumed inefficacy of immune-modulated therapies in sarcomatoid RCC, this histologic subtype was often treated with conventional chemotherapy combining doxorubicine, gemcitabine, and other chemotherapeutic agents. However, the doxorubicine+gemcitabine protocol reported important toxicity rates (61% of toxicity grades 1/2, and 26% toxicity grades 3/4, with threatening myelosuppression and one death from heart failure) in the presence of limited benefit in terms of PFS or OS (3.5 and 8.8 months, respectively)[59].

Recently, a phase-II trial combining capecitabine, gemcitabine, and bevacizumab showed a PFS of 5.5 and median OS of 12 months for patients with sarcomatoid features, making the combination a potential treatment option despite the low ORR observed (20%)[60]. On the other hand, the combination gemcitabine + sunitinib demonstrated a time to progression of 5 months and an OS of 10 months in these patients, showing better outcomes in the subset of patients exhibiting >10% sarcomatoid features in comparison with those presenting ≤10% of sarcomatoid differentiation[61]. Finally, a meta-analysis including the data from 6 different studies using anti-VEGF and conventional chemotherapy demonstrated better response rates with conventional chemotherapy-based protocols (7.9-18.6% *vs.* 0-15.8%)[62].

Soon after approval targeted therapies such as sunitinib and pazopanib began to be used in the treatment of RCC with sarcomatoid features. The International Renal Cell Carcinoma Database Consortium (IMDC) reported the outcomes observed in 230 patients with RCC and sarcomatoid features of which 93% had received anti-VEGF therapy in the first line of treatment, showing a PFS and OS of 4.5 and 10.4 months, respectively. In addition, Kawakami et al[63] described a higher PD-L1 expression and higher CD8-positive cell density in those RCC presenting sarcomatoid differentiation when compared with grade 4 clear cell RCC, making ICIs a possibly interesting option in the treatment of sarcomatoid RCCs. In line with these findings, the KEYNOTE 426 study (axitinib+ pembrolizumab *vs.* sunitinib) reported on the outcomes of a total of 105 patients exhibiting sarcomatoid features, noting a response rate of 58.8%[64]. A subanalysis in the IMmotion 151 trial (bevacizumab+atezolizumab *vs.* sunitinib) included a total of 142 patients with sarcomatoid differentiation (142/915=15.5%) showing no statistical differences between sunitinib and the ICIs combination in terms of PFS or OS[65]. An update of the Checkmate 214 study showed response rates comparable between the combinations nivolumab+ipilimumab and axitinib+pembrolizumab *vs.* sunitinib (57% *vs.* 19.2%)[56].

Conclusions

The non-clear cell RCC group includes approximately 15 different entities histopathologically and genetically separated from clear cell RCC. This type of tumors is frequently excluded from clinical trials due to their infrequency and heterogeneity, making the experience regarding the treatment of advanced stages of the disease limited to small size samples included in prospective or retrospective phase-II trials providing low-level evidence. Neverthless, it seems that in comparison with clear cell RCC, nccRCCs exhibit worse response rates to either anti-VEGF or anti-mTOR targeted therapies. These agents are currently being used in combination with ICIs in the context of RCTs, and their results will probably change the paradigm of treatment in the nccRCC subset of patients in the same way that occured the clear cell counterpart. However, more effort will be required due to the infrequent presentation of these rare diseases, making cooperative endeavors the key of future developments in this regard. In addition, further genomic assays will be required to identify different molecular biomarkers that would serve as the basis for new treatment options or therapy schedules.

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