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Review Article

Sarcomatoid Renal Cell Carcinoma, or Renal cell carcinoma with sarcomatoid dedifferentiation: Review of literature

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Abstract

Our understanding of the biology and pathophysiology of renal cell carcinoma (RCC) has greatly improved over the last decade. Understanding the disease process has helped us discover new histological subtypes and develop newer therapeutic approaches.

Although it is considered a histological subtype of all renal cell carcinomas (RCC), sarcomatoid renal cell carcinoma (sRCC) has been shown throughout the few cases found in the literature that it has a poorer prognosis and seems to not benefit from its historical 1st line treatment which is targeted agents such as sunitinib.

In this article, we will look at the characteristics of sarcomatoid renal cell carcinoma (sRCC) and how various drugs are currently used to treat it.

This article also examines the immune system's role in allowing sRCC growth and how the immune system can be manipulated to reactivate cytotoxic immunity against sRCC.

Indeed, the expansion of immunotherapies approved for sRCC has generated a search for biomarkers that might be indicative of treatment response in sarcomatoid RCCs (sRCCs), such as PDL1 expression, suggesting a potential benefit from PD1 and/or PDL1 immune checkpoint inhibitors.

Abreviations

sRCC: Sarcomatoid Renal Cell Carcinoma; CPI : Check Point Inhibitor; VEGFi : Vascular endothelial growth factor inhibitor; TKPi : Tyrosine kinase pathway inhibitor

Introduction

Sarcomatoid renal cell carcinoma (sRCC) is a sarcomatoid dedifferentiation that can occur in all RCC histological subtypes and portends an especially poor prognosis. Patients with sRCCs often present with advanced or metastatic disease and rarely survive more than a year [1]. Sarcomatoid dedifferentiation is found in 5% of all RCCs cases.

Cytoreductive nephrectomy may be proposed in cases of metastatic disease, but the discovery of biomarkers such PDL1 in sRCC has allowed the use of immunotherapy as 1st line treatment.

Discussion

sRCC is an extremely rare dedifferentiation that can occur in any subtype of RCC and represents 1-15% of all kidney tumors [2-3].

As for all renal cancers, the overall median age ranges from 54 to 63 years, with a male to female ratio of 2:1, probably explained by historical smoking habits or the influence of sex hormones on tumor biology.

The sarcomatoid component is associated with a rapidly growing disease, with approximately 20% of patients with metastatic RCC harboring this dedifferentiation [4-6].

The prognostic role of TNM stage and metastatic status has been identified in most of the series, with median survival twice as important in localized disease than in metastatic disease.

The WHO and International Society of Urologic Pathology (ISUP) classify sRCC as grade 4

disease and, accordingly, the majority of sRCC patients present with advanced or high-stage disease.

The main metastatic sites, in decreasing order of prevalence, are the lung, bone, brain, liver,lymph nodes, and brain.

Clinically, the presentation of sRCCs varies depending on the disease's stage.

Most patients present with locally advanced or metastatic disease therefore, approximately 90% are symptomatic at presentation, and signs and symptoms are often non-specific and can consist of abdominal pain, hematuria, weight loss, fatigue, fever, or pulmonary manifestations [7-8].

There are no reliable imaging methods or signs capable of identifying sRCC do not exist. Overall, CT scans show very large, heterogeneous, highly vascularized lesions with areas of necrosis, and locoregional or even remote invasion.

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Other methods, such as MRI or PET-CT with 18F-fluorodeoxyglucose,have been studied, but their clinical usefulness has not yet been demonstrated.

Farrow [9] was the first to describe the histological architecture of sRCC. It is a mixed tumor with carcinomatous epithelial elements, reminiscent of the architecture of renal tumors, as well as typical elements of sarcoma.

The carcinomatous contingent most often identified in decreasing order of frequency is clear cell carcinoma, chromophobe, tubulopapillary, and finally carcinoma of the collecting tubes.

Histological diagnosis can prove to be difficult because the sarcomatoid component can be predominant, and the epithelial component is difficult to identify, which often requires additional immunohistochemical staining. The latter shows that the tumor cells are positive for cytokeratin, epithelial membrane antigen (EMA) and vimentin [4].

This microscopic binarity is also found at the macroscopic scale in nephrectomy parts, where a mixed appearance is observed comprising friable and multi-nodular areas related to the carcinomatous component and other more firm and fibrous areas related to the sarcomatous component. [4-9]

On average, the sarcomatoid contingent represents 45-50% of the tumor, depending on the series. However, data in the literature are insufficient to determine the prognosis of the disease according to the proportion of this contingent within the tumor [4].

In localized non-sarcomatoid RCCs, nephrectomy is a curative procedure [10-11]. However, the outcomes are less encouraging in patients with localized sRCCs [12,13]

The role of cytoreductive nephrectomy in metastatic sRCC is unclear, as retrospective data from existing reports are conflicting, and no randomized controlled study has its eventual benefit.

A major difficulty of this debate is that, given the low rates of sRCC detection on preoperative imaging and biopsy, most patients are not known to have sRCC until after nephrectomy is performed. Therefore, the benefits of cytoreductive nephrectomy remain unclear.

Chemotherapy has been considered in some phase II trials in which sRCC was treated as a real sarcoma. Doxorubicin and/or gemcitabine-based protocols have been proposed. The results were disappointing, with a median progression-free survival of 3.5 months and a survival of 8.8 months. [14]

The cases of good response under chemotherapy remain exceptional [15].

The two current pillars for the treatment of metastatic kidney disease are targeted therapies including vascular endothelial growth factor inhibitors (VEGFi), and checkpoint inhibitors (CPI), such as tyrosine kinase pathway inhibitors (TKPi), [18-19-20]. The former works by limiting tumor angiogenesis, whereas the latter are monoclonal antibodies directed against checkpoints of the immune system.

However, in most prospective studies evaluating the efficacy of these VEGFi, case selection excludes the sarcomatoid histological subtype because of its rarity [2]. In a retrospective series, the objective responses to treatment with VEGFi remained low (approximately 20%), with a better response to treatment when the sarcomatoid component was poorly represented. [16]

Currently, checkpoint inhibitors used in oncology target inhibitory receptors present on the surface of lymphocytes (CTLA4 and PD1) or their ligands (PD-L1, PD1 ligand), which mechanisms are shown in Figure 1 [17].

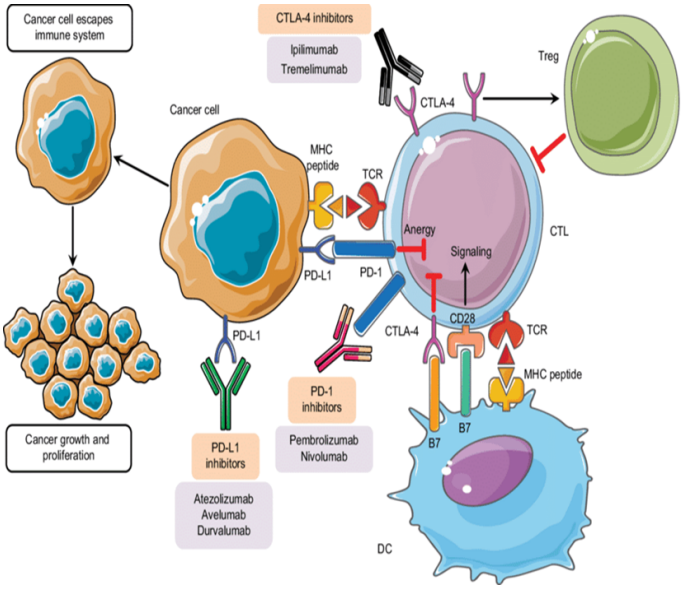

Figure 1. *Mechanisms of different immune checkpoint inhibitors*

Several studies have suggested that sRCC has diffuse PDL-1 expression in comparison with pure clear cell tumors.

This finding indicates that patients with sRCC may be good candidates for treatment with PD-1 / PD-L1 blockers rather than VEGFi.

Two molecules stand out: nivolumab, an IgG4 monoclonal antibody directed against cell death (PD-1), and ipilimumab, a recombinant IgG1 antibody that binds to cytotoxic T lymphocytes (CTLA-4).

In an essay published in 2018 in the European Urology Oncology [18], the primary objective was to assess overall survival in a series of 314 patients followed for metastatic RCC and already pretreated by a previous line based on CPI. These patients were then split into two cohorts: the first received an CPI followed by a targeted therapy, such as VEGFi-TKPi, while the second received an inhibitor of the m-Tor pathway. The study showed an improvement in overall survival and in progression-free survival in favor of the CPI + VEGF-TKPi group.

However, we note that among the criteria for including patients in most trials on CPI in metastatic renal disease, the presence of sarcomatoid differentiation is not specified [19].

Two recent studies have shown the benefit of treating metastatic sRCC with CPI: Checkmate 214 and Keynote 426.

In the randomized phase III trial CheckMate 214 [20], the investigators compared overall survival in 1096 patients followed for advanced RCC, divided into two groups: the first group received the combination iililumab + nivolumab, and the second received sunitinib.

The benefit in OS was in favor of the first group and was independently of the expression of PD-L1, with a hard ratio of 0.63. The results showed improving progression-free survival for patients treated with double CPI, with a hazard ratio of 0.82.

This benefit was more pronounced in the subpopulation with sarcomatoid differentiation. A complete response rate of 18.3% was also observed in the ipilumab + nivolumab arm versus 0% in the Sutent arm.

A study of its subgroup of 60 patients with sarcomatoid differentiation, showed an objective response of 56.7%, an overall survival of 31.2 months and a progression-free survival of 8.4 months, with an overall benefit in favor of the double CPI treatment.

Table 2. Efficacy Summary

	All Sarc		ITT[10]		PD-L1+Sarc		PD-L1+ ITT[10]	
	Atezo + Bev n = 68	Sunitinib n = 74	Atezo + Bev n = 454	Sunitinib n = 461	Atezo + Bev n = 36	Sunitinib n = 50	Atezo + Bev n = 178	Sunitinib n = 184
Median INV-assessed PFS (95% CI), mo[a]	8.3 (5.4, 12.9)	5.3 (3.3, 6.7)	11.2 (9.6, 13.3)	8.4 (7.5, 9.7)	8.6 (3.9, 15.3)	5.6 (3.3, 6.7)	11.2 (8.9, 15.0)	7.7 (6.8, 9.7)
Stratified HR (95% CI)	0.52 (0.34, 0.79)		0.83 (0.70, 0.97)		0.45 (0.26, 0.77)		0.74 (0.57, 0.96)	
Confirmed INV-assessed ORR (95% CI), %[a]	49 (36, 61)	14 (7, 23)	37 (32, 41)	33 (29, 38)	56 (38, 72)	12 (5, 24)	43 (35, 50)	35 (28, 42)
Ongoing responses, n	17	3	107	90	9	0	49	34
CR, %	10	3	5	2	14	4	9	4
Median OS (95% CI), mo[b]	21.7 (15.3, NE)	15.4 (10.4, 19.5)	33.6 (29.0, NE)	34.9 (27.8, NE)	19.3 (14.8, NE)	15.0 (8.4, 19.5)	34.0 (28.6, NE)	32.7 (23.3, NE)
Stratified HR (95% CI)	0.64 (0.41, 1.01)		0.93 (0.76, 1.14)		0.61 (0.35, 1.08)		0.84 (0.62, 1.15)	

Figure 1. *Differences in objective response in mRCC depending on PDL-1 status in IMmotion 151 Trial Presented at ASCO reunion in 2020*

Table 1. *Prospective trials assessing response toICPI in metastatic RCC*

Trial	Phase	Number of patients	Interventional Arm	Comparison Arm	OS (months)	PFS (months)
Atezolizumab	1	18	Atezolizumab	-	26	
CheckMate 214	3	139	Nivolumab+Ipililumab	Sunitinib	NR	26.5
Keynote 426	3	105	Pembrolizumab+Axitinib	Sunitinib	NR	NR
Javelin 101	3	108	Avelumab+Axitinib	Sunitinib	-	7
IMmotion 151	3	142	Atezolizumab+Bevacizumab	Sunitinib	21.7	8.3

With the advent of CPI, the indication for surgery can be discussed on a case-by-case basis, especially in metastatic disease, thus reducing the morbidity and mortality associated with surgery.

In the prospective Keynote 426 trial [21], 864 patients with newly diagnosed or recurrent stage 4 RCC were randomized to receive either pembrolizumab + axitinib or sunitinib. The primary endpoints were OS and PFS. And it was the case in the Chekmate 214 trial, the improvement in both primary endpoints was obtained in the cohort of patients treated with Pembrolizumab+Axitinib, with a hazard ratio of 0.53 in terms of OS, and 0.69 in terms of PFS.

Finally, the IMmotion 151 trial [22] is a randomized phase III study comparing atezolizumab plus bevacizumab versus sunitinib in patients with metastatic RCC with either complete clear cell or sarcomatoid components. The latter case represented 16% of all patients.

In the sarcomatoid population, the objective response rate in patients receiving atezolizumab + bevacizumab was significantly higher than that for those receiving sunitinib (49% vs. 14%), as shown in figure 2.

The results of these major trials have provided new conclusions concerning stage 4 RCC :

-VEGFi treatment (sunitinib) is no longer the standard of care.

-A combination of treatments is more effective and improves OS.

-TKPi should be the standard second-line treatment

The major prospective trials that helped us with these conclusions are in Table 1.

Conclusion

sRCC is a rare cancer, most often discovered late,with a very poor prognosis.

The lack of data highlights the need for continued research into the biology, diagnostics, and treatment options of patients with this disease.

Reports of higher expression of PD1 and PDL1 in sRCCs than in non-sarcomatoid RCCs have generated growing interest in immune checkpoint blockade therapies in combination with other systemic agents.

The future will focus on personalized treatment using molecular biology, which will allow us to specifically target the altered molecular pathways involved in the genesis of this cancer.

Each case must be discussed individually in an onco-urology multidisciplinary consultation meeting to choose the best therapeutic combination with the fewest side effects.

Large collaborative prospective and specific trials are needed to improve the understanding of this disease to propose more effective treatments for this lethal disease.

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FO wrote the article, MAC made critical assessments of the article, and NT supervised the work. All authors have read and approved the final version of the manuscript.

Authors' information

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Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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