World Journal of Urology (2019) 37:115–123
https://doi.org/10.1007/s00345-018-2355-y

INVITED REVIEW

Epidemiology, biology and treatment of sarcomatoid RCC: current state of the art

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Received: 28 March 2018 / Accepted: 25 May 2018 / Published online: 1 June 2018

Abstract

Long recognized to confer an extremely poor prognosis, sarcomatoid dedifferentiation of renal cell carcinoma (sRCC) is a tumor phenotype that is finally beginning to be better understood on the molecular and genetic levels. With an overall incidence that ranges from 1 to 32% depending on associated RCC subtype, the survival of sarcomatoid RCC patients rarely exceeds 2 years. The main reasons for its poor outcome include its aggressive biology, its tendency to present at an advanced or metastatic stage at the time of diagnosis, its high rate of tumor recurrence after nephrectomy, and its limited response to systemic therapies. Molecular pathology studies suggest that sarcomatoid dedifferentiation originates from a focal epithelial–mesenchymal transition (EMT) arising in the carcinomatous component of the tumor. It is hoped that the growing understanding of the molecular biology of sRCC will soon make it possible to adapt treatments based on the identification of actionable tumor alterations. The deliberate inclusion of these patients in the multicenter clinical trials of immune, targeted and combination therapies is a necessary next step in pioneering future treatment strategies.

Keywords Sarcomatoid renal cell carcinoma · Kidney neoplasms · Immunotherapy

Introduction

Renal masses comprise a biologically heterogeneous group of tumors ranging from benign neoplasms to a diverse group of malignancies that range from rare mesenchymal and hematologic malignancies to a family of epithelial cancers. They can be further stratified into distinct histologic subtypes some of which behave in a relatively indolent manner and those that are highly aggressive and lethal. Worldwide, nearly 270,000 new cases of renal cell carcinoma (RCC) are diagnosed annually, and about 116,000 patients die each year. These estimates include 115,000 new RCC cases per year in Europe and 64,000 in the United States [1, 2].

In 2012, the International Society of Urological Pathology (ISUP) Grading System for renal cell carcinoma grouped sarcomatoid and rhabdoid tumors, giant cell tumors and tumors with extreme nuclear pleomorphism into a single category of grade 4 tumors [3]. Sarcomatoid transformation, once considered to represent a distinct histological subtype, is now correctly recognized instead as a common pattern of "dedifferentiation" with loss of characteristic epithelial features of RCC. This dedifferentiation can often be found in association with an epithelial component of RCC regardless of primary subtype [3].

In recent years, antiangiogenic, immunologic, and other targeted therapies have demonstrated improved progression-free survival (PFS) and overall survival (OS) for patients with metastatic RCC (mRCC) in several phase III clinical trials. However, the efficacy of these targeted therapies is limited in patients with sarcomatoid RCC (sRCC) [4–6]. To better understand the current management and future research directions of sRCC, we present the current state of the art for this extremely aggressive malignant pathology.

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Methods

We searched MEDLINE® for articles in English language published up to March 2018 using the keywords "Carcinoma, Renal Cell" [Mesh], "Kidney Neoplasms" [Mesh], "kidney cancer", "sRCC", and "sarcomatoid". ClinicalTrials.gov was queried for ongoing studies. Relevant data presented at main urology and medical oncology meetings are also included.

Results

Epidemiology

Sarcomatoid dedifferentiation of RCC affects younger patients than RCC without sarcomatoid features with an average age of 56–61 years, and a male-to-female ratio ranging between 1.6:1 and 2.2:1 [7–9]. It accounts for 1–32% of all forms of kidney cancer depending on epithelial subtypes: 5–13% of clear cell RCC (ccRCC), 2–7% of papillary RCC, 9–13% of chromophobe RCC, 11–26% of unclassified RCC, and nearly 29% of the collecting duct carcinomas (CDC) [10–12]. Among individuals with metastatic disease, it is identified in nearly 20% of the cases [13].

Clinical features and imaging

In contrast to RCC without sarcomatoid features which are often asymptomatic and incidentally diagnosed, a high proportion (86–89%) of patients with sRCC are symptomatic. Frequent symptoms at presentation include pain (51–52%), hematuria (22–34%), and systemic symptoms such as weight loss (18–22%), fatigue (15%), fever/night sweats (6–12%), and cough/dyspnea (6%). Patients with sRCC generally present at higher stage than patients with RCC without sarcomatoid features, as evidenced by a higher rate of locally advanced (T3–T4) disease (56–80 vs. 23%), regional lymph node involvement (13–62 vs. 16%) and distant metastases (45–81 vs. 16%) at presentation [1, 6, 8, 10, 13–15].

While paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs, less is known about the types and incidence of paraneoplastic syndromes in sRCC [16].

An infiltrative appearance and irregular contour on radiographic imaging suggest high-grade tumor of the kidney, including those with sarcomatoid features. In a study by Young et al. on multiphasic multidetector computed tomography, sRCC and CDC were more likely to have an irregular contour and an infiltrative spread pattern than other solid renal masses. An infiltrative spread pattern had a specificity of 93% and sensitivity of 82% to differentiate sRCC and CDC from other solid renal masses. An irregular contour had a specificity of 98% and sensitivity of 64%. Other tumors in the kidney, however, can also have an infiltrative spread pattern, such as sarcomas, transitional cell carcinomas, lymphomas, and metastases, as well as medullary carcinomas in patients with sickle cell trait [17].

Pathology

Sarcomatoid dedifferentiation within carcinomas is a well-known phenomenon in various organs (i.e., lung, bladder, penile), including the kidney. Sarcomatoid carcinoma is not a specific morphogenetic subtype of RCC but is considered as a pattern of dedifferentiation, and is a distinct tumor from other rare tumors such as sarcoma of the kidney and sarcomatous urothelial tumors [3, 7].

Macroscopically, sarcomatoid areas appear as dense gray/white areas with an invasive margin and a firm, fleshy-to-fibrous cut surface [18]. Mean diameters of tumor usually range from 9.2 to 11 cm, indicating it often reaches a large diameter by the time of surgery [8, 11]. Histologic coagulative tumor necrosis is observed in up to 90% of tumors [10].

Unlike a true sarcoma, microscopically, sRCC contains both epithelial (carcinoma) and mesenchymal (sarcomatoid) components (Fig. 1), and in a sRCC one is nearly always able to find a component of conventional RCC with enough sections to allow for a correct diagnosis. When only sarcomatous elements are present, special studies, such as immunohistochemical stains, may be needed to help distinguish epithelial tissues having a sarcomatoid appearance from true mesenchymal elements. Dense fibrotic stroma is often observed. The mesenchymal component takes on a highly variable appearance mimicking any sarcoma constituting various histological subtypes of sRCC: the fibrosarcoma-like pattern, the fibrous histiocytoma like, in addition to other patterns such as the hemangiopericytoma, chondrosarcoma, malignant histiocytofibroma and even rhabdomyosarcoma. The leiomyosarcoma, which is the most frequent type of classical sarcoma of the kidney, has a unique appearance that should not be confused for sRCC. The most usual form of the sarcomatoid component is the presence of a fusiform, spindle tumoral contingent, within a mostly necrotic and hemorrhagic area [3, 18]. There is no accepted threshold to assign a RCC as a sRCC, and in fact any sarcomatous elements should be reported as such, with the sarcomatoid feature expressed as a percentage of the tumor.

Sarcomatoid elements are observed in the metastases of primary tumors with sarcomatoid features. However, both sarcomatoid and epithelial components can metastasize in the same patient. Biopsy of the primary tumor or a metastatic site detects the presence of sarcomatoid features in only 7.5% of cases, likely because sarcomatoid features

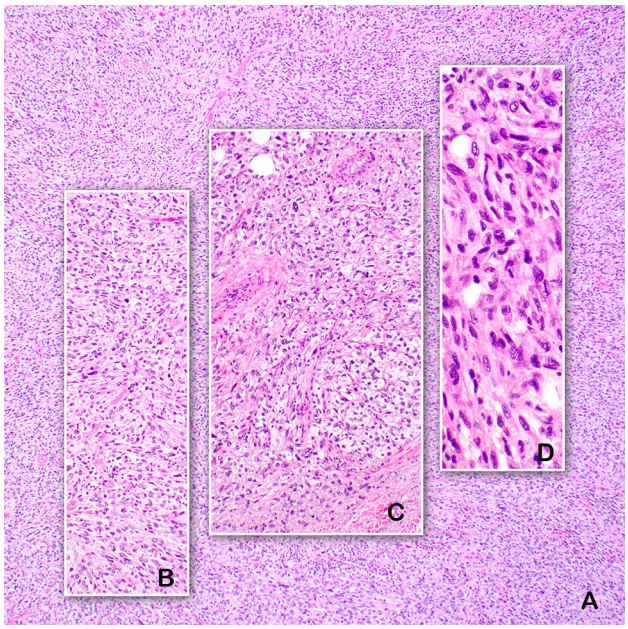

Fig. 1 **a** Sarcomatoid renal cell carcinoma demonstrating dense sheets of spindle cells. H&E, ×40 magnification **b**: Tumor cell spindling with moderate nuclear pleomorphism. H&E, ×100 magnification **c** Sarcomatoid renal cell carcinoma invading perinephric fat and arising from clear cell renal cell carcinoma (bottom right). H&E, ×100 magnification **d** High-magnification image of sarcomatoid renal cell carcinoma. Tumor cells are spindling and show moderate nuclear pleomorphism. There are scattered mitotic figures present. H&E, ×400 magnification

often comprise a small focal area of growth within a greater tumor which may be missed by a random biopsy sampling [6]. Patients with > 30% sarcomatoid features in the primary tumor frequently have sarcomatoid histology in a metastatic site [13].

Low-grade spindle cell proliferation (LG-SCP) is a part of morphologic heterogeneity in ccRCC and do not represent an initial stage of sarcomatoid differentiation [19]. Regions of rhabdoid differentiation are reported in around 15% of tumors classified as sRCC [20].

Molecular pathogenesis

The sarcomatoid dedifferentiation appears to originate from the so-called epithelial–mesenchymal transition (EMT). EMT is a biologic process in which epithelial cells gradually lose an epithelial phenotype and gain a mesenchymal one, leading to spindle cell morphology, increased motility, invasive capacity, high resistance to apoptosis and increased production of extracellular matrix proteins [21].

Loss of heterozygosity (LOH) and X-chromosome inactivation data support the contention that both the clear cell and sarcomatoid tumor components in RCC arise from a common cell of origin, and that clonal divergence occurs during tumor progression with subpopulations of neoplastic cells acquiring unique genetic alterations leading to the observed EMT [22]. Cytogenetic data show relative preservation of truncal chromosomal abnormalities between RCC without sarcomatoid features and sarcomatoid morphology as well as matched metastatic settings [23].

A study by Sircar et al. suggests that biphasic epithelial and sarcomatoid components of sarcomatoid ccRCC are similar at the DNA copy number and transcript levels but are markedly different from non-sarcomatoid ccRCC. These elements of similarity suggest a model in which the major division occurs between the broad categories of sarcomatoid and conventional ccRCC, and where most of the genetic programming for sarcomatoid ccRCC is embedded in its epithelial component [24].

According to a recent study by Bi et al., the sarcomatoid component has common mutations not seen in the epithelial areas. In particular, sarcomatoid elements had biallelic tumor protein p53 (TP53) mutations in 32% of tumors, whereas TP53 mutations were rare in ccRCCs. Mutations in known cancer drive AT-rich interaction domain 1A, and BRCA1-associated protein 1 (BAP1), were mutually exclusive with TP53 and with each other. From the tumors of 21 subjects analyzed in this study, two tumors had hypermutation consistent with mismatch repair deficiency. One hypermutated tumor contained an R175H alteration in TP53, a known gain-of-function mutation that results in up-regulation of TWIST1, a significant EMT transcriptional regulator [25]. Malouf et al. [26] identified frequent mutations of NF2 that were mutually exclusive with TP53 mutations.

Wang et al. studied 40 frozen sRCC samples segregated according to the parent subtype rather than the epithelial or sarcomatoid morphologic components. In agreement with the clinical and pathologic supposition, the Wang data support the concept that sRCC is not a single entity but rather multiple diseases that segregate according to the underlying parent subtype. Conventional ccRCC is characterized by a very high frequency of biallelic VHL inactivation caused by allelic deletion or LOH on chromosome 3p21–25 [27]. In contrast, sarcomatoid ccRCC appears to have a distinct tumorigenesis, generally lacking copy losses at 3p21–25 [28]. In the same study, nine genes were found to have significant, recurrent mutations across all sRCC samples: VHL, C10orf113, PTEN, TP53, BAP1, NF2, TMEM97, CALML3, and IL15. RELN mutations were significantly higher in sRCC across all subtypes [28]. RELN encodes the protein Reelin, which is an essential negative regulator in the TGFβ1-induced cell migration process, as knockdown increased migration and overexpression prevented TGFβ-induced migration. Furthermore, Reelin expression is controlled by Snail, a master regulator of EMT, and knocking down Reelin leads to increased expression of mesenchymal markers [29].

On the other hand, the expression of Aurora kinase A (AURKA) is increased in sarcomatoid tissue compared to their benign or clear cell parts. The increase in AURKA correlated with increased mTOR pathway activity, as evidenced by increased expression of phosphorylated mTOR (S2448) and ribosomal protein S6K (T389) [30].

An immunohistochemical study by Yu et al. showed that sRCC conserved expression of vimentin, a type III intermediate filament protein that is characteristically expressed by mesenchymal cells, though 80% of cases also showed immunostaining for at least one epithelial marker, such as CK, EMA, CK7, and CK18. Notably, expression rates of markers for RCC such as CAIX, CD10, and PAX8 in sarcomatoid cells remained high at 76, 76, and 64%, respectively. PAX8, with an extensive expression in both carcinomatous and sarcomatoid cells, has been suggested to be used as a useful diagnostic marker for identifying the RCC with sarcomatoid differentiation in needle aspiration cases [31]. In a series of 20 patients with sRCC, the sarcomatoid component was positive for c-Kit in 18 cases (94.7%) with high c-Kit expression. This finding may imply that Imatinib targeted therapy could be an option for these tumors [32]. The biological aggressiveness of sRCC is supported by the proliferative marker Ki-67 with expression higher in sarcomatoid than in clear cell or papillary tumors (25 vs. 9%) [33].

A better understanding of sRCC biology may come from other techniques such as microRNA expression, epigenetic regulation, post-translational modification and micro-environmental influences of the kidney tumor as well as metastases.

Prognosis

Patients with sRCC present with more advanced disease and demonstrate a higher rate of cancer-specific mortality. In recent series, sRCC had a median OS ranging from 10 months to 2 years (and up to 30 months in a small immunotherapy series) depending on metastatic status at initial diagnosis (Fig. 2) [5, 6, 34–37]. Depending on performance status and tumor characteristics (localized or metastatic), multimodal approaches can be considered to improve treatment outcome. Identifying sarcomatoid component is an independent predictor of lymph node invasion, a decreased time-to-recurrence with a relative risk of 5.87 for metastasis at 3 years following RN [38–40]. In a series of 77 patients with sRCC, 56 (72%) of the 73 patients who were free of

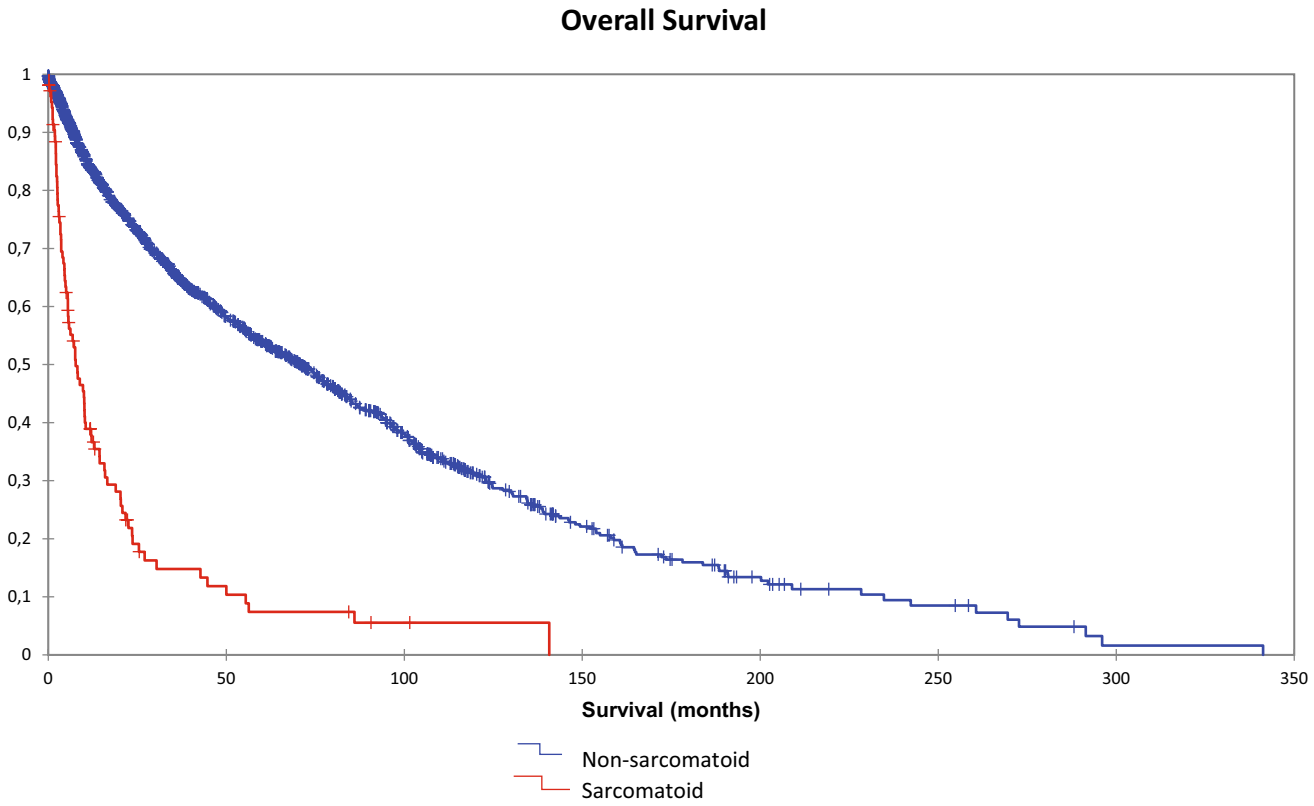

Fig. 2 Illustrative Kaplan–Meier analysis of a UCLA cohort, comparing survival of 106 patients with sRCC and 1639 patients with RCC without sarcomatoid features (all stages). Mean overall survival times of patients with or without sarcomatoid features RCC were 20 months (95% CI 13.28–28.06) and 93 months (95% CI 86.51–100.38), respectively ($p < 0.0001$)

disease after RN, experienced a recurrence, with a median time to recurrence of 26.2 months [41]. Once metastatic, metastasectomy is not considered beneficial [42]. Moreover, the underlying epithelial subtype has an impact on cancer-specific survival (CSS). Non-clear cell histology is associated with lower CSS than conventional clear cell histology and is an independent predictor of cancer-specific death [6, 34].

For patients undergoing cytoreductive nephrectomy, the presence of sarcomatoid dedifferentiation confers a dire prognosis despite aggressive surgery and postoperative therapy [9, 43]. They have a high rate and a shorter time to relapse, worse baseline prognostic criteria, and no apparent long-term benefit with targeted therapy [6, 36, 43]. Based on a predictive risk model established by Shuch et al., microvascular invasion, the percentage of sarcomatoid features and necrosis are significant predictors of survival [14]. Several studies have established a percentage of sarcomatoid component threshold (50 or 30%) for the response to targeted therapies and the higher the overall sarcomatoid component rate, the worse the response to targeted therapies. However, this might not be accurate when considering a combination of VEGF-targeted therapies with chemotherapy (better response if > 10%) [4, 11, 14, 44, 45]. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic models have been applied to patients with sRCC [6, 36].

Treatment modalities of localized sRCC

Nephrectomy and adjuvant therapy

Although the American Urological Association (AUA) recommends prioritizing partial nephrectomy (PN) for small renal masses when possible, sRCC rarely presents (13% in a SEER-based study) with a tumor that is amenable to nephron-sparing approaches [46]. In most cases, radical nephrectomy (RN) should be preferred over PN due to the high rate of locally advanced tumors and the infiltrative appearance that can often be observed on pre-operative imaging. Because of its propensity to exhibit poor capsule formation and microscopic and microvascular invasion, PN may place the patient at increased risk of local recurrence, and thus RN may provide an oncologic advantage [47].

Sunitinib has been studied in the post-nephrectomy adjuvant setting for high risk of recurrence renal cell carcinoma with conflicting results [48–50]. The S-TRAC study has allowed an FDA-expanded approval of Sutent to reduce the risk of kidney cancer recurrence [49]. The clinical trials reporting the effect of adjuvant therapy have not explicitly investigated such treatments on sRCC. A subgroup analysis of the S-TRAC study identified a Fuhrman grade 3 or 4 tumor group was in favor of sunitinib (HR 0.73, 95% CI 0.55–0.98) [51]. In ASSURE trial, sarcomatoid features were observed in 51 (8%) patients in sunitinib group, 58 (9%) cases in sorafenib group and 61 (10%) in the placebo arm. Subgroup analysis of Fuhrman grade 4 did not favor adjuvant therapy with a hazard ratio of 1.05 (IC 0.73–1.53) [48]. With pazopanib, in PROTECT trial, patients with sRCC were not detailed, and no subgroup analysis was available. We are waiting for results of ongoing studies including patients with sRCC tumors.

Strategies for post-surgery surveillance should be based on the risk of recurrence. Different postoperative scores have been applied to assess prognosis in RCC, which are used for risk-adapted follow-up strategies, including the University of California Integrated Staging System (UISS) and the Mayo Clinic Scenario, Size, Grade, and Necrosis (SSIGN) [40, 52]. Though there are no guidelines specifically designed for the follow-up of sRCC tumors, the presence of sarcomatoid features found at the time of nephrectomy necessitates integration of a Fuhrman grade 4 into the tumor's risk category.

Treatment modalities of metastatic sRCC

There are no specific guidelines for the management of patients with sRCC. Few studies have demonstrated modestly improved response rates in patients receiving targeted therapy, chemotherapy (or a combination of those) or immunotherapy. Other therapies are under evaluation. Those treatments are not targeting the sarcomatoid features, but the different histologies and essentially all treatments overlap.

Targeted therapy

Kyriakopoulos et al. reported a series of 230 patients with sRCC and compared them with 2056 patients with RCC without sarcomatoid features. More than 93% of them received VEGF inhibitors as first-line therapy. Objective response was less frequent in sRCC (21 vs. 26%), and primary refractory disease was more common (43 vs. 21%). The median PFS and OS were 4.5 and 10.4 months, in sRCC patients compared to 7.8 and 22.5 months, in RCC without sarcomatoid features patients, respectively [36].

Golshayan et al. examined a series of 43 patients with sRCC who were treated with VEGF-targeted therapies. Median PFS and OS were estimated to be 5.3 and 11.8 months, respectively. Six patients (28%) achieved a partial response (PR). These patients had tumors showing a sarcomatoid component which represented < 20% of the neoplastic tissue [4].

Keskin et al. compared survival of sRCC patients who had nephrectomy and received systemic therapy in the cytokine era (1987–2005, $n = 122$) or the targeted therapy era (2006–2015, $n = 77$). A total of 69.9% of the cases presented

with metastatic disease at initial diagnosis. Although a significant improvement in survival rate was observed in the first year for patients treated in the targeted therapy era, this effect was attenuated after 2 years, disappeared 3–5 years after diagnosis, and was not evident in patients with poor risk features [6].

Kunene et al. reported a series of 23 patients with sRCC treated with sunitinib. PFS and OS were 5.7 and 15.7 months, respectively. Sunitinib showed efficacy particularly in patients with good performance status (PS). The median OS of patients with PS 0–1 was 20.9 vs. 5.0 months with PS 2–3 [53].

Voss et al. reported a series of 23 sarcomatoid ccRCC patients treated with mTOR inhibitors either temsirolimus or everolimus, with 65% of the cohort being pretreated. PFS and OS were 3.5 and 8.2 months, respectively. Overall, patients responded poorly, three patients (13%) achieved a PR, and an isolated patient achieved disease control for ≥ 12 months [54].

Compared to RCC without sarcomatoid features, targeted therapies have a relative effect at best in sRCC with a PFS range from 4.4 to 5.7 vs. 10.4 months in non-sRCC and OS range from 10 to 20.9 vs. 22.5 months in non-sRCC. The therapies targeting VEGF pathway may be more effective in patients with good performance status.

Chemotherapy

Rapid growth and pathologic resemblance with sarcomas have generated interest in cytotoxic chemotherapy for sRCC. In the ECOG8802 phase II study, the combination of gemcitabine and doxorubicin in 38 patients with previously untreated advanced or metastatic sRCC showed an objective response rate (ORR) of 16%. Median PFS and OS were 3.5 and 8.8 months, respectively. This study suggested that patients whose tumors had a higher percentage (> 75%) of sarcomatoid component might benefit the most from cytotoxic therapy, irrespective of the underlying subtype [55].

Another phase II study had evaluated doxorubicin and ifosfamide in 23 patients with metastatic sRCC. No objective response was observed. In six cases, the disease was considered stable at the end of chemotherapy. Time to progression (TTP) and OS were 2.2 and 3.9 months, respectively [56].

Combination of antiangiogenic therapy and cytotoxic chemotherapy has been studied in two phase II clinical trials [44, 57–59]. Combination of sunitinib and gemcitabine was studied in 39 patients with metastatic sRCC. The ORR was reported at 26%, and TTP and OS were 5 and 10 months, respectively. Patients whose tumors had > 10% sarcomatoid component had an improved clinical benefit rate (Chemical–biological–radiological (CBR) response, ORR + stable disease rate) compared to patients with ≤ 10% sarcomatoid histology (CBR 100% for > 10 vs. 55% for ≤ 10% sarcomatoid, $p = 0.04$) [44, 57].

Combination of capecitabine, gemcitabine, and bevacizumab was studied in 34 patients with metastatic or unresectable sRCC. ORR was 20% (five partial responses, one complete response), and disease control rate was 73%. Time to treatment failure, PFS, and OS were 4.2, 5.5 and 12 months, respectively [58].

Overall, phase II trials with chemotherapy have inconsistent results in sRCC with a PFS range from 2.2 to 5.5 months and OS range from 3.9 to 12 months. Combination of VEGF-targeted therapy with chemotherapy such as sunitinib with gemcitabine for sRCC patients appear to be promising with a better response threshold of > 10% sarcomatoid component.

Immunotherapy

Historical series support the responsiveness of sRCC to high-dose interleukin-2 (HD IL-2) [60]. In a series of 31 patients managed by surgical resection and HD IL-2-based immunotherapy, OS at one and 2 years was 48 and 37%, respectively. The relative risk of death adjusted for age, sex, and sarcomatoid component less than 50%, for patients not receiving any IL-2, was 10.4 times higher than for patients receiving IL-2 [45]. In 2017, Achkar et al. reported a series of 21 patients with metastatic sRCC treated with HD IL-2 following nephrectomy. The ORR was 10%, with a 5% complete response. Localized disease at presentation was associated with a better response to HD IL-2. Median PFS and OS with HD IL-2 was 7.9 and 30.5 months, respectively [37].

The sRCC's response to checkpoint inhibitors is expected to be reported in ongoing trials, but two case reports have documented a rapid response to the PD-1 inhibitor nivolumab in patients with sRCC. The first one was a chromophobe sRCC that was pretreated with chemotherapy (doxorubicin and ifosfamide) and presented with a recurrence in the tumor bed after debulking surgery. After six cycles of nivolumab, a partial response was observed [61]. The second case was a metastatic papillary RCC with sarcomatoid and rhabdoid components with failed treatments with carboplatin/gemcitabine, then sunitinib, and finally gemcitabine with a rapid progression. At 3 weeks after a single dose of nivolumab at 0.3 mg/kg, there was a clinical, biological and radiological response [62].

The PD-L1 inhibitor, atezolizumab, was evaluated in a phase Ia study of pretreated patients with ccRCC. Among 18 patients who demonstrated either Fuhrman grade 4 or sarcomatoid histology, an encouraging response rate of 22% was observed [63].

SRCC has been shown to express PD-1/PD-L1 at a higher rate than RCC without sarcomatoid features. Joseph et al. examined 26 cases of sRCC compared to a cohort of 29

Table 1 Ongoing and unpublished studies in patients with sRCC or advanced RCC with sarcomatoid features

Clinical identifier	Study type	Drug	Setting
NCT03288532 (RAMPART)	Phase III	Durvalumab ± tremelimumab vs. current standard	Adjuvant
NCT03142334 (KEYNOTE-564)	Phase III	Pembrolizumab vs. placebo	Adjuvant
NCT03138512 (CheckMate 914)	Phase III	Nivolumab and ipilimumab vs. placebo	Adjuvant
NCT03024996 (IMmotion010)	Phase III	Atezolizumab	Adjuvant
NCT03055013 (PROSPER)	Phase III	Nivolumab vs. observation	Peri-operative
NCT02420821 (IMmotion151)	Phase III	Atezolizumab and bevacizumab vs. sunitinib	Metastatic or unresectable
NCT02853331 (KEYNOTE-426)	Phase III	Pembrolizumab and axitinib vs. sunitinib	Advanced or metastatic or recurrent
NCT03141177 (CheckMate 9ER)	Phase III	Nivolumab and cabozantinib vs. nivolumab and ipilimumab and cabozantinib vs. sunitinib	Advanced or metastatic
NCT03177239 (UNISoN)	Phase II	Nivolumab, then combination ipilimumab + nivolumab	Metastatic or unresectable non-ccRCC
NCT02724878	Phase II	Atezolizumab and bevacizumab	Metastatic or unresectable non-ccRCC
NCT01164228	Phase II	Sunitinib and gemcitabine or sunitinib	Unresectable sRCC
NCT02853344 (KEYNOTE-427)	Phase II	Pembrolizumab	Advanced or metastatic
NCT01767636 (PINCR)	Phase II	Pazopanib	Metastatic
NCT03097328	Phase II	Sapanisertib	Metastatic
NCT00126503	Phase I/II	Sorafenib and bevacizumab	Advanced

cases of conventional ccRCC. PD-1 expression was examined on tumor-infiltrating lymphocytes as well as the PD-L1 expression on tumor cells. The presence of PD-1 expression was identified in 96% sRCC cases in contrast with 62% in ccRCC. Similarly, PD-L1 expression was identified in 54% sRCC and 17% of conventional ccRCC cases. Co-expression of both PD-1 and PD-L1 was identified in 50% of sRCC cases, compared to 1 case (3%) in the ccRCC cohort [64]. Overall, these findings suggest that the PD-1/PD-L1 axis could be an essential target when considering therapeutic options in sRCC.

Ongoing studies

Several clinical trials are evaluating targeted treatment, immunotherapy or chemotherapy, and combinations in patients with metastatic or advanced RCC with sarcomatoid features. A summary of these studies is presented in Table 1.

Conclusion

Sarcomatoid dedifferentiation of RCC appears to be a general phenomenon that presents with the common features of epithelial–mesenchymal transition, but which appears on the molecular level to represent not a single entity but rather multiple diseases that segregate according to the underlying parental epithelial subtype. Although this phenomenon is observed in only a minority of renal cancers, its management remains a challenge due to its aggressive behavior and poor response to existing therapies. Currently, no standardized recommendations exist among urological or oncologic guidelines due to its low incidence rate and lack of disease-specific trials from which one normally establishes consensus on treatment. The growing understanding, however, of its molecular biology and underlying genetic and epigenetic pathways, will hopefully allow future, prospective multi-institutional studies to address more intelligently designed questions regarding optimal therapeutic strategies for this disease process.

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