Sarcomatoid Renal Cell Carcinoma: A Comprehensive Review of the Biology and Current Treatment Strategies

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Key Words. Sarcomatoid • Renal cell carcinoma • Kidney cancer

Learning Objectives

After completing this course, the reader will be able to:

1. Describe histologic features associated with sarcomatoid renal cell carcinoma.
2. Outline current surgical approaches to treating sarcomatoid renal cell carcinoma.

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Abstract

Recent advancements in the molecular characterization of renal cell carcinoma altered the classification system and now kidney cancer is divided into several distinct histologic subtypes. Although once a separate histologic category, sarcomatoid renal cell carcinoma is no longer considered a separate tumor type because it can occur with all histologic subtypes. Limited research on tumors with sarcomatoid change has led to minimal progress in the understanding and treatment of these tumors. Because the sarcomatoid variant of renal cell carcinoma can account for approximately one in six cases of advanced kidney cancer, we hope to familiarize clinicians with these tumors by describing the historic background, histologic features, molecular characterization, diagnosis, prognosis, treatment strategies, and active clinical trials of this aggressive type of tumor. *The Oncologist* 2012;17:46–54

Introduction

The past two decades have seen dramatic changes in our understanding and management of renal cell carcinoma (RCC). The molecular alterations associated with several individual histologic subtypes of kidney cancer have now been characterized, leading to the development of rational targeted therapeutic strategies. The characterization of the familial kidney cancer syndromes, such as von Hippel-Lindau disease, hereditary leiomyomatosis and RCC, hereditary papillary RCC, and Burt-Hogg-Dubé syndrome, gave valuable insight into the biology of their sporadic counterparts [1–7]. Thus, both approved and investigative anticancer agents now focus on the dysfunctional cellular biology rather than as in the prior era of nonspecific immunotherapy or chemotherapeutic agents. However, one specific RCC entity, sarcomatoid RCC (sRCC), remains to be fully characterized and therefore remains a

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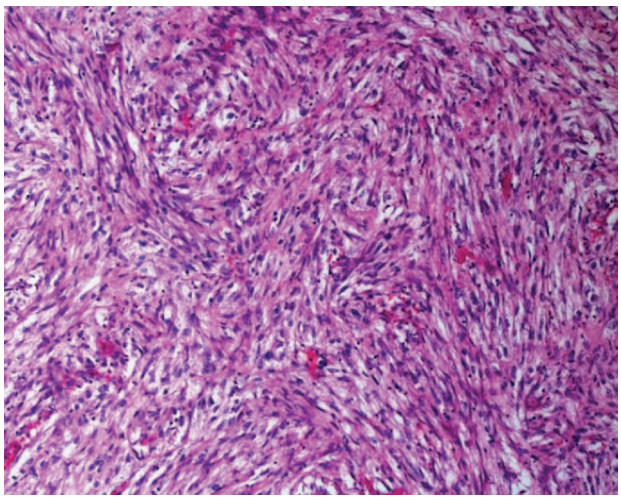

Figure 1. Sarcomatoid renal tumor displaying elongated, spindle-shaped cells, high cellularity, and cellular atypia. This clear cell renal tumor had 70% sarcomatoid features and the patient presented with lung, nodal, and colon metastases.

poorly treatable and highly lethal form of kidney cancer. Although accounting for only ~5% of RCCs, the aggressive nature and advanced stage of presentation makes sRCC fairly common to practitioners who manage patients with metastatic disease [8, 9]. To allow practitioners to better understand sRCC, we present a comprehensive review of the current thinking on the biology and treatment of this tumor.

History

Renal tumors with sarcoma-like appearances were characterized by pathologists as renal sarcomas in the early half of the 20th century [10]. However, many pathologists began to recognize classic RCC characteristics in many of these tumors. These findings ultimately led to a change in the nomenclature of renal sarcomas to a different term, carcinosarcoma of the kidney. Eventually the term sRCC was established and was considered a separate histologic type because of its highly aggressive nature [11]. A separate subtype for sRCC, however, was questioned by pathologists with the recognition of sarcomatoid changes in association with every histologic type of renal tumor. Updated classification schemes in the late 1990s disbanded this category and considered sRCC to be a feature related to extensive chromosomal rearrangements [12, 13]. It was believed that these rearrangements led to identical spindle-cell morphology regardless of the primary epithelial histology. Delahunt et al. [14] later termed sarcomatoid characteristics the "final common dedifferentiation pathway" for renal tumors. Although now reclassified by the American Joint Committee on Cancer and Heidelberg pathology schemes, many urologic and medical oncologists consider sRCC to be a clinically relevant grouping because of the cohort's poor prognosis and its relative resistance to multiple forms of systemic therapy [8, 9].

Histologic Characteristics

sRCCs contain features similar to sarcomas, with spindle-like cells, high cellularity, and cellular atypia (Fig. 1). Regions of sarcomatoid transformation do not have noticeable epithelial components; wavy or rhabdoid regions that maintain epithelial features should not be considered sarcomatoid [9]. These regions of sarcomatoid change may be uniform or heterogeneous. Common uniform histologic patterns can resemble fibrosarcoma or malignant fibrous histiocytoma; however, osteoid or chondroid differentiation has been described [8, 15, 16]. These uniform patterns of sarcomatoid differentiation and the degree of pleiomorphism do not appear to influence clinical behavior [9, 15]. Additional high-risk tumor characteristics such as necrosis and microvascular invasion are present in 90% and 30% of cases, respectively [8, 9].

The majority of tumors have a variable amount of recognizable carcinoma elements, in the range of 1%–100%, with a mean and median of ~40%–50% [8, 17]. In the absence of recognizable carcinoma areas, the pathologist should consider cutting additional tumor blocks for a more thorough assessment. Frequently, the high degree of necrosis in sRCC makes recognition of the histology challenging, and therefore it is not uncommon to look at large numbers of blocks in order to determine a recognizable carcinoma component.

The epithelial component may originate from any of the well-described RCC histologic types. Because of the high incidence of clear cell RCC, this histology is associated with >80% of sRCCs [8, 11, 17]. Some series, however, have reported the highest frequency of sarcomatoid transformation to be in patients with chromophobe RCCs, rather than papillary and clear cell tumors [9, 18]. Unclassified RCC accounts for 2%–10% of sRCCs depending on the series [8, 9, 17]. The majority of these cases represent tumors with 100% sarcomatoid histology and no recognizable epithelial component; however, occasionally an unclassifiable epithelial component may be present, leading to this designation. It is uncertain if identifying the primary histology will alter prognosis or treatment outcome. In two series including mostly patients treated prior to the targeted therapy era, the carcinoma histology did not appear to dictate clinical behavior [8, 19].

Although sRCCs are typically associated with high-grade tumors, this entity is also seen with low-grade tumors. A study by Ro and colleagues demonstrated that >30% of sRCCs were associated with a Fuhrman 1/2 RCC [15]. Such findings can fuel speculation that the rise of the sarcomatoid pattern may not represent a continuum of dedifferentiation from classic RCC, but rather result from activation of a separate sarcomatoid stem cell within the tumor.

Although sRCCs may resemble classic sarcomas, important differences are recognizable. First, primary renal sarcomas are extremely rare in adults, accounting for <1% of renal malignancies. When they do occur, almost half are leiomyosarcomas, which contain smooth muscle components that are rarely observed in sRCCs [20]. Additionally, primary renal sarcomas should not contain any classic areas of RCC [8]. Other tumors that may mimic sRCCs are sarcomatous urothelial tumors. These may be distinguished by

the presence of flat in situ regions and/or squamous differentiation.

For confirmation of the diagnosis of sRCC, additional tests may be performed, including electron microscopy (EM) and immunohistochemistry (IHC). With EM, the epithelial components of sRCCs (such as desmosomes or the basal lamina) not observed by classic light microscopy may be visualized [21, 22]. IHC for common epithelial and mesenchymal markers may distinguish sRCC from sarcoma. A review of IHC staining of sRCCs by DeLong and colleagues demonstrated that the sarcomatoid areas still express cytokeratin AE1/AE3 and vimentin in 97% and 56% of cases, respectively [23]. Classic markers observed in mesenchymal tissue and sarcomas, such as desmin and actin, are infrequently expressed in sRCCs.

Molecular Characterization

The molecular characterization of sRCCs has been limited for a wide variety of reasons. The majority of studies addressing this question have used whole tumors rather than the sarcomatoid portion. If sarcomatoid transformation does represent an aggressive clone that is terminally dedifferentiated, an assessment of this tumor component alone must be performed. Tumor heterogeneity may, therefore, have caused flaws in the design of some studies and obscured findings specific to sarcomatoid cells. The advanced nature and rapid progression of disease have limited the available number of patient samples for analysis. Also because sRCCs can arise from all renal epithelial subtypes, studies combining multiple histologies make interpretation difficult. Because there may be different molecular events associated with each histology, it may be beneficial to focus on one particular subtype that undergoes sarcomatoid change.

Tumor Aggressiveness/Proliferative Index

Although it is thought that the sarcomatoid component represents a different and more biologically aggressive entity, limited evidence supports this assumption. Although groups have demonstrated low-grade carcinoma adjacent to highly pleiomorphic sarcomatoid components, there are many cases in which either tumor component can metastasize [15, 24]. It is unclear if these low-grade lesions represent a tumor with distinct phylogeny or they share a clonal origin.

Several studies have looked at the proliferative index of sRCC to make inferences regarding its biologic aggressiveness. However, several of those studies included data from whole tumor specimens. The initial studies conducted in this manner demonstrated that sRCCs have a higher proliferative rate than other renal tumors based on Ki-67 staining or other proliferative markers [25, 26]. However, if compared with other high-grade tumors, sRCCs demonstrate similar high proliferative indices [27]. Later studies comparing tumor components demonstrate a greater number of mitotic figures in the sarcomatoid region [15]. In an evaluation of 11 sRCCs, Kanamaru and colleagues demonstrated that the sarcomatoid component had a higher Ki-67 expression level than the carcinoma component [28].

Cytogenetic Alterations

A few early studies demonstrated unique cytogenetic changes associated with sRCC. However, the inclusion of multiple histologic subtypes and whole tumor specimens makes interpretation of these studies difficult. Jiang et al. [29] performed comparative genomic hybridization on 12 sRCC tumors and found large numbers of chromosomal changes (mean, 8.6; range, 0–20), with losses occurring more frequently than chromosomal gains. Common losses occurred on 13q (75%) and 4q (50%). In 2002, Dal Cin and colleagues examined the cytogenetic profile of four sRCC tumors. The cytogenetic profile of sRCCs did not resemble conventional cytogenetic profiles for clear, papillary, and chromophobe RCCs, leading the authors to conclude that sarcomatoid tumors arise from tumors with a different biology [30].

Brunelli and colleagues evaluated chromophobe RCCs with and without sarcomatoid transformation [31]. This histologic subtype frequently dedifferentiates into sRCC for unclear reasons [9, 18]. Of the six sRCCs evaluated, there were cytogenetic differences between tumor components in four (66%). There were multiple gains at chromosomes 1, 2, 6, 10, and 17 in both components, distinct from other aggressive, chromophobe tumors used as controls, suggesting that sRCCs may arise from chromophobe tumors with a distinct biology [31].

To assess the clonal origin of sRCCs, Jones and colleagues evaluated 22 patients with clear cell sRCC tumors [32]. Analysis of X-chromosome inactivation between components confirmed a common progenitor cell in 13 of 14 tumors from female patients. Analysis of loss of heterozygocity at five microsatellite polymorphic markers found different patterns of allelic loss between components in the majority of cases. These findings led the authors to conclude that the sarcomatoid component represents a divergent clone [32].

Protein Signature

IHC of both sarcomatoid and nonsarcomatoid tumor components in sRCC specimens has been performed in several studies. Tickoo and colleagues assessed the expression of important members of the hypoxia-inducible factor (HIF) pathway (HIF-1α, vascular endothelial growth factor [VEGF], glucose transporter 1, and carbonic anhydrase IX) in 34 sRCCs [33]. Tumors arising from clear cell histology maintained high HIF pathway expression in the sarcomatoid regions, whereas those from nonclear-cell tumors continued to have limited expression. These findings suggest a common cell of origin/common biology between tumor components. Additionally, these findings suggest that targeted VEGF agents could demonstrate activity in sRCC treatment.

Other limited studies suggested greater expression of FAS ligand, c-KIT, and S6-kinase in sRCCs [34–36]. However, a large study from the Mayo Clinic disputes the importance of C-KIT in sRCCs. Less than 5% of a large cohort of sRCC patients had expression of c-KIT, and positive tumors had no evidence of mutation on direct sequencing [37].

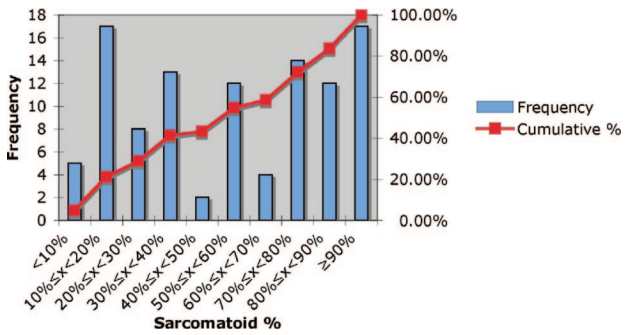

Figure 2. Histogram demonstrating the wide variability in the percentage of sarcomatoid histology in the primary tumor in 104 patients with sarcomatoid renal cell carcinoma. Unpublished data from UCLA, used with permission from A. Belldegrun.

Mutational Analysis

There have been limited mutational analyses performed with sRCCs. Oda and colleagues demonstrated that the sarcomatoid component had a higher frequency of *p53* mutations than the carcinoma component. In an analysis of 14 tumors (four with clear cell components), 11 of 14 (79%) demonstrated *p53* mutations in the sarcomatoid component, whereas only two of 14 (14%) had mutations in the adjacent carcinoma component [38]. However, a more recent study assessing p53 protein expression provided an argument against this finding. Kanamaru and colleagues observed low p53 protein expression in both tumor components from 11 tumors, suggesting that *p53* mutations are not a major determinant of sarcomatoid change [28]. However, the sensitivity of IHC for *p53* mutation detection is only 85%, so it is possible that this method of analysis missed mutations in this small cohort.

Clinical Presentation

The presentation of kidney cancer varies widely and is dependent on the stage at diagnosis. In most published series, sarcomatoid tumors are usually extremely large, with a mean tumor size of 9–10 cm, and ~90% are symptomatic at presentation [15, 23, 39–41]. The incidence of metastatic disease is extremely high at presentation, with 45%–84% having evidence of systemic disease [9, 39, 42]. Metastases occur at similar locations as with other renal tumors, with the most common sites of distant disease being the lungs, bone, nodes, liver, and brain, respectively [42]. One series did report a high incidence of bone metastases, but a recent series showed a similar 29% rate of bone involvement for sRCCs and nonsarcomatoid RCCs [17, 43].

Preoperative Identification

Because most patients with sRCCs typically have rapidly progressive disease, it may be of clinical utility to identify these patients prior to a cytoreductive nephrectomy. For distant lesions resected prior to nephrectomy, the presence of sarcomatoid histology may predict the presence of sarcomatoid features in the primary tumor. However, an evaluation of distant sites of metastasis from sRCC demonstrated that >30% of distant lesions contained only high-grade carcinoma elements. Therefore, the absence of sarcomatoid features at the time of metastasectomy has a low specificity in predicting the presence of a primary tumor with sarcomatoid histology [24].

Fine-needle aspiration (FNA) and standard core biopsy are other potential ways to diagnose renal tumors. Although Auger and colleagues reported that sRCCs can be reliably diagnosed using FNA in conjunction with IHC, others have argued that FNA of any renal mass should not be performed [44]. For patients who do need a tissue diagnosis, core biopsy has emerged as a safe and reliable way of identifying renal malignancy and may replace FNA [45].

Identification of sarcomatoid histology on biopsy is limited by several factors. First, the amount of tissue obtained from a 16- to 18-gauge core biopsy is limited and may be nondiagnostic for large masses [46]. Secondly, the tumor heterogeneity of sRCCs can lead to sampling error because over half of these tumors contain <50% sarcomatoid features (Fig. 2) [17]. Finally, it is not known if the histologic architecture after fixation and processing can be sufficiently maintained for a pathologist to reliably distinguish sRCC from high-grade carcinoma or sarcoma. Wood and colleagues at MD Anderson Cancer Center recently demonstrated that only 10% of sRCC patients who underwent nephrectomy had this histology demonstrated on preoperative renal biopsy [46].

Prognosis

Patients with sRCC appear to have the worst prognosis of all renal tumor patients. Few patients demonstrate extended survival; those who do generally present with early-stage disease (stage I and stage II) [8]. The majority of series report a median survival time of only 4–9 months after diagnosis [9, 17, 39, 41, 43]. Compared with other patients with high-grade RCCs, those with sRCCs still have a worse prognosis. Multiple series have confirmed the presence of sarcomatoid features to be an independent predictor of poor survival [9, 47, 48]. The presence of sarcomatoid components may be one of the most influential prognostic variables for patient outcome [17]. Several studies have looked at the effect of the percentage of sarcomatoid transformation on prognosis and demonstrated that greater amounts were associated with a worse outcome [8, 9, 17]. However, there is no agreed upon cutpoint for risk stratification at this time.

Local Management/Role of Surgery

As mentioned above, there is no reliable preoperative method of identification to determine if a renal tumor is an sRCC [17]. However, if identified on biopsy or a future molecular/imaging modality, there are several important management considerations. The aggressive nature of these tumors argues against any observation strategy. Although ablative techniques such as cryotherapy and radiofrequency ablation have emerged as an option for small renal masses, there is no evidence supporting their use in this population and it should be cautioned. Upfront nephrectomy remains the standard of care for all patients with localized renal tumors, with a strong emphasis on renal pres-

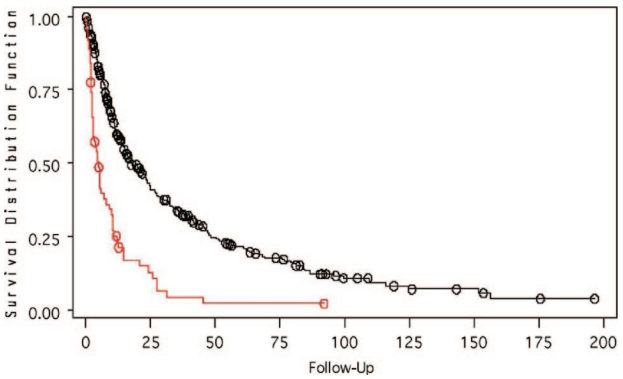

Figure 3. Kaplan–Meier analysis of overall survival in months after cytoreductive nephrectomy for sarcomatoid (red) and non-sarcomatoid renal cell carcinoma. Adapted from Shuch B, Said J, La Rochelle JC et al. Cytoreductive nephrectomy for kidney cancer with sarcomatoid histology–is up-front resection indicated and, if not, is it avoidable? J Urol 2009;182:2164–2171, with permission.

ervation when possible [49]. Partial nephrectomy has rarely been used for sarcomatoid tumors because of the large, bulky nature of this disease. If recognized preoperatively and partial nephrectomy is attempted, clinicians may face unexpected surprises resulting from the disease biology. These tumors may demonstrate rapid interval growth and/or dissemination, and recent imaging must be performed prior to intervention. The infiltrative nature of these tumors may make achievement of a negative margin difficult, and enucleative surgery should not be considered in this population.

For most sRCC patients who present at an advanced stage with a large, bulky tumor, surgery can be very challenging, and generally radical nephrectomy is required. Frequently, these tumors are associated with an intense desmoplastic reaction and resection of adjacent organs may be required. In a series of patients undergoing cytoreductive nephrectomy, >25% of them had T4 disease and 33% had positive lymph nodes [17]. As such, significant morbidity may be unavoidable in advanced cases.

Although lymph node dissection in the absence of clinical disease has been omitted because of level I evidence [50], Blute and colleagues at the Mayo Clinic recommended extended lymph node dissection if sarcomatoid features are identified at the time of surgery [51].

In the setting of metastatic RCC, level I evidence supports the benefits of cytoreductive nephrectomy prior to planned immunotherapy [52, 53]. Although the new era of targeted therapy has demonstrated responses in the primary tumor, cytoreductive nephrectomy often remains an integral part of therapy [54]. Whereas cytoreductive surgery still has a major role in the treatment of metastatic RCC, for patients with sRCC, many question the survival benefit of cytoreductive surgery [17, 39]. The aggressive nature of this disease may result in rapid disease progression with delayed initiation of systemic therapy to allow for postoperative convalescence [55]. Previous experience with these patients has indicated that ~60% cannot proceed to systemic therapy after surgery [17]. In the absence of any reliable preoperative evidence of sRCC, it may be unavoidable to proceed with a cytoreductive nephrectomy. However, if we are able to detect these tumors with either a biopsy or resection of a distant metastasis, available data suggest that upfront surgical resection may be of little or no benefit. In this setting, we propose an algorithm in which we would consider the patient for a trial of upfront systemic therapy and reserve surgery only for those patients with a good performance status who exhibit a clinical response. Although there is no level I evidence to support this method, there is plenty of evidence that the strategy of upfront surgery in this patient population leads to an abysmal outcome (Fig. 3) [17, 39].

Systemic Therapy Experience

Patients with sRCC have limited systemic therapy options and regimens have met with extremely poor results (Table 1). In an early series, Sella and colleagues at MD Anderson Cancer Center reported their experience with sRCC in 44 patients [43]. A variety of chemotherapy, immunotherapy, and hormone therapy regimens was used and led to median survival times of 6–12 months. Notably, there were two patients who obtained a complete response with doxorubicin-based chemotherapy and, additionally, four patients treated with interferon-α had a median survival duration of 41 months [43]. This changed the treatment approach to focus on combination immunochemotherapy regimens.

The University of California at Los Angeles Kidney Cancer program published their initial experience with interleukin-2–based therapy in 31 patients with sRCC. The response rate of 21% (complete response, 6%; partial response, 15%) was similar to that seen in other immunotherapy series at the time [56, 57]. The 1- and 2-year overall survival rates were quite encouraging, at 48% and 37%, respectively. However, the initial success failed to continue because updated series from this institution demonstrates that sarcomatoid histology is an independent predictor of poor survival and response to therapy [58]. Kwak and colleagues also assessed the prognosis of patients who received different immunotherapy regimens. Those authors demonstrated a worse survival outcome for those with sarcomatoid histology receiving immunotherapy. Although not randomized, there did not appear to be any survival advantage with immunotherapy because the median survival times were 10.0 months for those on therapy and 9.0 months for those receiving no therapy [59]. Although there was no mention of the response rate in that series, there were no long-term survivors in the immunotherapy arm.

Because chemotherapy plays a role in the management of a variety of sarcomas, its use in sRCC patients has been explored for the past two decades. As mentioned above, the report by Sella et al [43] demonstrated several complete responses with chemotherapy that included doxorubicin. Later, Culine and colleagues reviewed their experience with chemotherapy and found several responses with doxorubicin administration [60]. That experience led Escudier et al. [61] to organize a multi-institution phase II trial of combination doxorubicin and ifosfamide. The results of that series were disappointing: of the 23

Table 1. Systemic therapy experience with sarcomatoid renal tumors

Study	Treatment	Clinical trial?	*n*	Response (CR/PR)	Objective response	%
Sella et al. (1987) [43]	Medroxyprogesterone 17-acetate + androgen therapy	No	6	0/0	0	0.0%
	Cyclophosphamide, vincristine, doxorubicin, and dacarbazine	No	8	2/0	2	25.0%
Mian et al. (2002) [39]	INF-α + fluorodeoxyuridine	No	10	0/2	2	20.0%
	INF-α + 5-FU	No	43	0/18	18	41.9%
	Cyclophosphamide, vincristine, doxorubicin, and dacarbazine	No	6	0/1	1	16.7%
	INF-α/IL-2 + 5-FU	No	14	0/18	6	42.9%
Nanus et al. (2004) [62]	Gemcitabine + doxorubicin	No	10	2/1	3	30.0%
Escudier et al. (2002) [61]	Doxorubicin + ifosfamide	Yes	23	0/0	0	0.0%
Cangiano et al. (1999) [42]	HD IL-2	No	9	0/2	2	22.2%
	LD IL-2 + INF-α + TIL	No	9	1/2	3	33.3%
Golshayan et al. (2009) [66]	Sunitinib	No	26	0/6	6	23.1%
	Sorafenib	No	12	0/1	1	8.3%
Staehler et al. (2008) [65]	Gemcitabine + doxorubicin	No	15	0/0	0	0.0%
Haas et al. (2009) [64]	Gemcitabine + doxorubicin	Yes	38	1/5	6	15.8%
Michaelson et al. (2010) [67]	Gemcitabine + sunitinib	Yes	9	0/3	3	33.3%
			238	6/47	53	22.3%

Treatments of $n \geq 5$ found in the literature are shown.
Abbreviations: 5-FU, 5-fluorouracil; CR, complete response; HD, high dose; IL-2, interleukin-2; INF-α, interferon-α; LD, low dose; PR, partial response; TIL, tumor-infiltrating lymphocytes.

patients enrolled, no clinical responses were observed and the median survival duration was <4 months [61]. In 2004, Nanus and colleagues reported some clinical responses with gemcitabine and doxorubicin combination therapy. In an analysis of 10 patients with sRCC treated with this regimen, three responses were seen, including one complete response. Of the two partial responders, one was rendered free from disease after surgical excision of retroperitoneal disease [62]. Those authors recently updated their experience with several of the long-term survivors. Complete responses with this treatment appear durable because two patients with a prior complete response remained alive and disease free at 6 years and 8 years [63].

The encouraging results from the 2004 report by Nanus and colleagues led to a prospective, phase II study, Eastern Cooperative Oncology Group (ECOG)-8802, evaluating the efficacy of gemcitabine in combination with doxorubicin in patients with previously untreated advanced sRCC. Haas and colleagues recently presented the data from that study involving 38 patients. Overall, the cohort had median progression-free survival (PFS) and overall survival (OS) times of 3.5 months and 8.8 months, respectively. Several responses were observed (one complete and five partial responses; objective response rate, 16%) and the regimen was fairly well tolerated, with only two patients stopping treatment as a result of toxicity [64].

Several centers initially adopted chemotherapy for patients with these tumors, but with the availability of VEGF-targeted therapy, there has been an attempt to evaluate the efficacy of this class of agent in sRCC therapy. Staehler and colleagues evaluated sorafenib in 15 patients who had progressed on gemcitabine plus doxorubicin; there were no responses to chemotherapy and the median time to progression was 6.6 months. However, sorafenib appeared to have some activity in this population, with a mean time to progression of 10.9 months, and one of 15 (7%) patients had an objective response. These findings led the authors to conclude that antiangiogenic therapy should be further explored in sRCC patients [65].

Golshayan and colleagues at the Cleveland Clinic recently reported on a large retrospective series of patients ($n = 43$) with sRCC treated with tyrosine kinase inhibitors or bevacizumab. Partial responses were observed in 19% of patients, with the majority of responses observed in tumors with clear cell histology [66]. The median PFS and OS times were 5.3 months and 11.8 months, respectively, slightly higher than those seen in prior chemotherapy series [43, 61]. An interesting finding noted in that series was that patients with a limited

amount of sarcomatoid change in the primary tumor (<20%) appeared to have a better outcome with VEGF therapy.

Active Clinical Trials

The majority of the newly approved targeted agents have mainly been tested in patients with clear cell RCC. A coordinated effort at studying the less common histologic types of kidney cancer, including sarcomatoid tumors, will enable identification of mechanism-based therapeutic approaches to distinct subtypes of RCC. Referral to centers participating in clinical trials for these rare tumor types is of vital importance in expediting accrual and improving our understanding of the optimal treatment strategies for these patients. Several studies involving sarcomatoid tumors are currently enrolling patients at various centers in the U.S.

A phase II trial at Dana Farber Cancer Institute and Beth Israel Deaconess Medical Center is investigating combination therapy with sunitinib plus gemcitabine in patients with either sarcomatoid histology or poor-risk features by the Motzer criteria. Patients receive 3-week cycles during which sunitinib is administered for the first 2 weeks and gemcitabine is given on days 1 and 8. Michaelson et al. [67] recently reported the initial experience with this regimen at the 2010 American Society of Clinical Oncology Genitourinary Cancer Symposium. Of the first nine patients with sRCC, three patients had a partial response and the median time to progression was 4.6 months.

An ongoing phase II clinical trial at MD Anderson Cancer Center is currently investigating a combination regimen involving bevacizumab, capecitabine, and gemcitabine. During this 4-week cycle, patients receive daily capecitabine for the first 3 weeks and an infusion of bevacizumab and gemcitabine on days 1 and 15. Enrollment is ongoing, with a goal accrual of 40 patients.

ECOG 1808 is a recently opened trial that is examining sunitinib with or without gemcitabine for patients with sRCC. That phase II study aims to accrue 100 patients and is stratifying patients based on the percentage of sarcomatoid features in the primary tumor. Six-week cycles of treatment include sunitinib (days 1–15 and days 22–35) and gemcitabine (days 1, 8, 22, and 29) for patients in the chemotherapy arm.

Conclusions

sRCC is an important entity for all clinicians to be familiar with. Because this entity may account for 10%–20% of patients with advanced disease, it continues to be a major contributor to RCC mortality. The sarcomatoid component may represent a terminally dedifferentiated clone arising from any of the conventional histologic subtypes of RCC or it may arise from a completely separate clone. Surgery in the setting of localized disease is the standard of care, but adjuvant trial participation should be considered because of the high-risk for recurrence. So far, cytoreductive nephrectomy has not been shown to be beneficial because of rapid disease progression during convalescence and the low probability of receiving systemic therapy, although this has not been studied in a randomized fashion. Unfortunately, today there is no reliable method to detect this histology preoperatively. There may be a role for combination chemotherapy with antiangiogenic therapy in sRCC treatment, but the ultimate improvement will come from better molecular and genetic characterization of sRCC and design of specific therapies.

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Collection and/or assembly of data: Brian Shuch
Data analysis and interpretation: Ramaprasad Srinivasan, Brian Shuch
Manuscript writing: Ramaprasad Srinivasan, Brian Shuch, W. Marston Linehan, Gennady Bratslavsky
Final approval of manuscript: Ramaprasad Srinivasan, Brian Shuch, W. Marston Linehan, Gennady Bratslavsky

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