A 51-Year-Old Man With Rapidly Progressive Metastatic Sarcomatoid Renal Cell Carcinoma: An Apparent Complete Clinical Response to Second-Line Therapy With Sunitinib and Low-Dose Interferon-Alpha

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Case Report

A 51-year-old white man presented to our clinic in January 2006 for evaluation of a 14-cm left renal mass (Figure 1), which extended into the perinephric fat (see Figure 2 for a graphic representation of this complex history). The mass was surgically removed in February and determined to be a grade IV renal cell carcinoma (RCC) with 5% sarcomatoid differentiation. Multiple pulmonary and mediastinal metastases identified by computed tomography initially regressed following nephrectomy. However, by March 2006, the disease had rapidly progressed, with the development of metastases in the left proximal humerus, the right proximal tibia, and the head of the right femur. The femoral metastasis was treated with external irradiation, while the metastasis in the left proximal humerus was surgically removed. Massive tumors, one of which is shown in Figure 3, also developed bilaterally in the gluteal muscles; these masses were treated with cryoablation.

Chemotherapy initially stabilized the disease and consisted of doxorubicin and gemcitabine at doses of 50 mg/m^2 and 1,500 mg/m^2, respectively, according to the protocol developed by Nanus and colleagues.[1] Unfortunately, the patient had progression of his cancer after 6 cycles, with the development of widespread metastases and severe hypercalcemia. Doxorubicin and gemcitabine were therefore discontinued. At that time, evidence suggested that therapy with interferon-α and sorafenib (Nexavar, Bayer) may provide clinical benefit[2]; however, sunitinib (Sutent, Pfizer) had been shown to possess greater clinical efficacy than sorafenib.[3] Consequently, in August 2006, the patient was initiated on 3 million units (MU) subcutaneous interferon-α 3 times per week, 5 weeks on, 2 weeks off, and 50 mg oral sunitinib daily, 4 weeks on, 2 weeks off. The patient was treated with a cumulative dose of 235 mg/m^2 doxorubicin prior to this change.

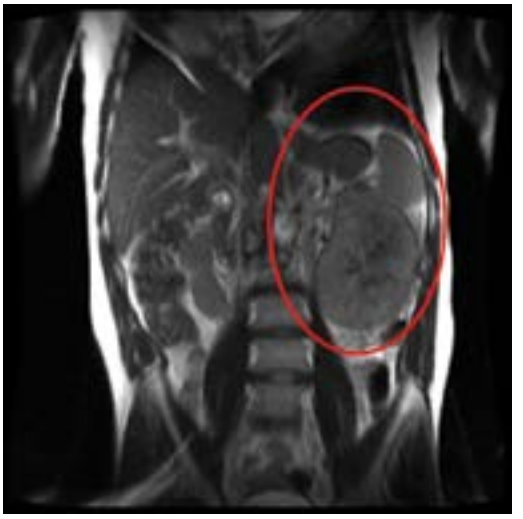

Figure 1. Magnetic resonance image of the presenting left renal mass. This mass measured approximately 14.6 × 9.6 × 13.0 cm.

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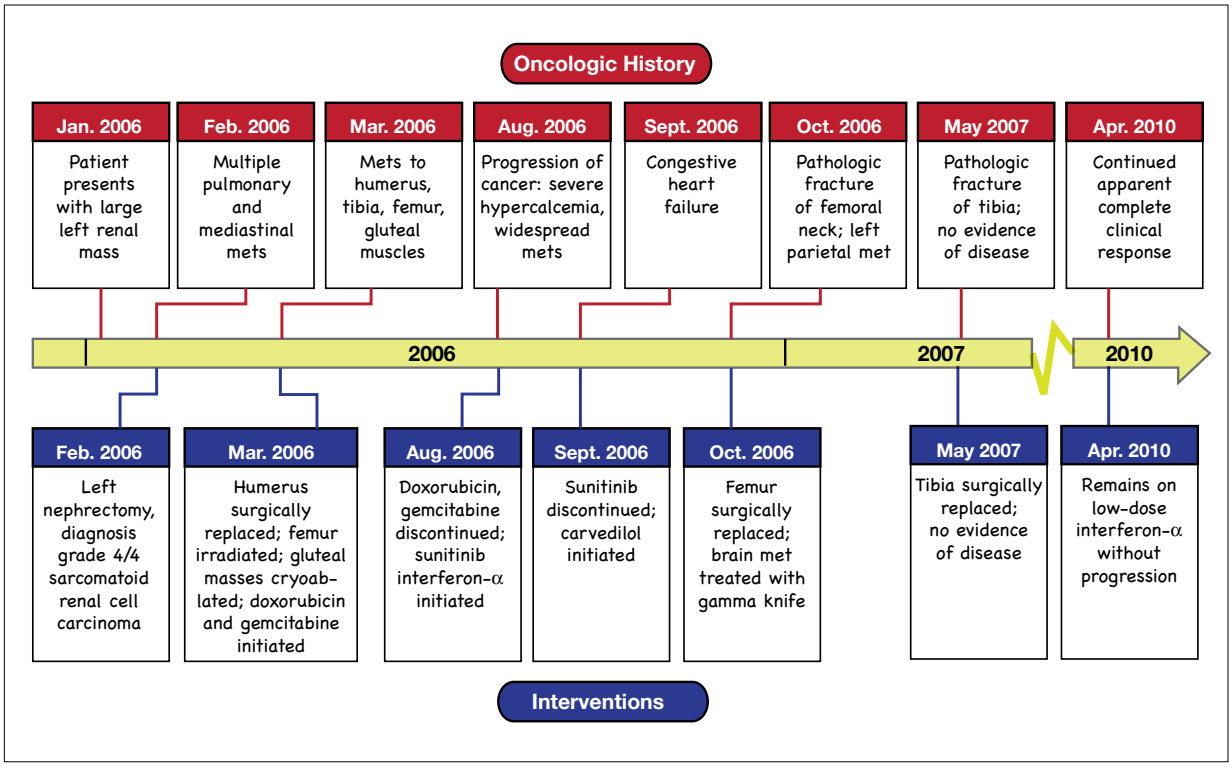

Figure 2. Timetable of events. The oncologic history is depicted above, and the interventions below.

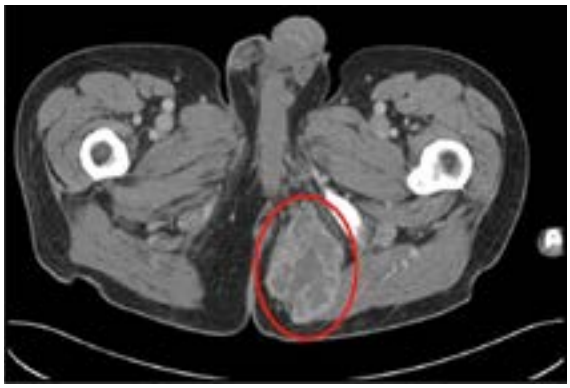

Figure 3. Computed tomography of a large metastasis in the left gluteal muscle. The mass measured approximately 6.9 × 5.3 × 6.4 cm. The mass abuts the medial margin of the left gluteus maximus muscle and extends superiorly into the ischiorectal fossa. This mass was treated with cryoablation and subsequently resolved, apart from some residual pain reported by the patient, which may represent residual disease undetectable by computed tomography (see text).

Approximately 1 month later, the patient developed congestive heart failure (CHF) secondary to his therapy, and he required hospitalization. Enalapril (an angiotensin-converting enzyme inhibitor) and carvedilol (a calcium channel antagonist) were initiated with improvement. The patient's left ventricular ejection fraction (LVEF) nadir was in the 10–15% range, but gradually improved with pharmacologic intervention and has stabilized at 40–45%. Given its cardiotoxic side effects,[4] sunitinib was discontinued, while low-dose interferon-α treatment was maintained. In October 2006, the patient suffered a pathologic fracture of the right femoral neck, in the location of a prior metastasis, which required surgical removal and arthroplasty. The patient then developed a 2.3-cm metastasis, with significant vasogenic edema within the left parietal lobe, which was subsequently treated with stereotactic radiosurgery.

In May 2007, the patient suffered another pathologic fracture of his right tibia, where he had previously had a metastasis, which, upon surgical intervention, was found to contain no evidence of disease. Nearly 4 years later, the patient continues to have an apparent complete clinical response and remains on maintenance low-dose interferon-α as described above. In general, the patient states that his quality of life is good, his performance status is a 0–1, and he is able to maintain a moderate exercise routine.

Discussion

Sarcomatoid RCC is a rare and aggressive cancer that is associated with a poor prognosis. Sarcomatoid differentiation is found in approximately 1–8% of RCCs,[5] although estimating incidence is difficult, as clinical studies often do not report the number of patients with sarcomatoid differentiation.[6] Median overall survival is 3–10 months,[7-10] and the 5-year survival rate is low, at 19%.[6,11,12]

Sarcomatoid RCC can arise from any of the RCC subtypes (clear cell, chromophobe, collecting duct, papillary, and unclassified),[13] and is thought to represent a progression to a higher histologic grade.[6] Further support for an epithelial origin arises from the finding that sarcomatoid RCCs usually stain positively for AE1/AE3 and MUC1. In addition, vascular endothelial growth factor (VEGF) is an important target for therapy and is expressed in a majority of these tumors,[5] as is hypoxia-inducible factor, an upstream activator of VEGF.[14]

Historically, treatment of sarcomatoid RCC has been challenging. Interferon-α, an immune modulating agent with antiangiogenic and antiproliferative properties, has been employed in a number of clinical trials[7,10,15] and has also been investigated retrospectively in the treatment of sarcomatoid RCC,[8] although trends in treatment are shifting away from interferon-α.[16] Doxorubicin and gemcitabine have been central to the oncologist's armamentarium since a definitive study performed by Nanus and colleagues in 2004.[1] The development of receptor tyrosine kinase inhibitors that target neoangiogenesis (sunitinib, in particular) has brought a modestly improved clinical response in recent studies.[6,17] A recent phase III clinical trial has also demonstrated improved quality of life for patients treated with sunitinib versus interferon-α (9 MU 3 times per week).[18]

Second-line therapy for sarcomatoid RCC has not been defined. Given the highly aggressive and resistant nature of this disease, the establishment of an effective and tolerable alternate therapy is desperately needed. The authors are unaware of any case reports or studies investigating the efficacy of low-dose interferon-α and sunitinib in sarcomatoid RCC. Considering the patient's very positive response to this regimen, the combination employed here may be a novel and effective second-line therapy in sarcomatoid RCC.

We postulate that the antiangiogenic effects of sunitinib were effective in the initial regression of the patient's cancer, while the immune-modulating activity of low-dose interferon-α was responsible for the patient's continued stabilization. Intriguingly, the patient stated that during attempts to discontinue his interferon-α treatments for more than 3 weeks, he had discomfort in his gluteal regions in the locations of the large masses previously treated with cryoablation. This suggests that there may be residual disease in this region, which is being stabilized by the immune-modulating properties of interferon-α.

Considering the patient's congestive heart failure (CHF), certain precautions should be taken in the application of this therapeutic approach. Patients should be evaluated for risk of CHF, and titrated to a tolerable dose of sunitinib with monitoring of LVEF percent throughout treatment. Previous significantly cardiotoxic chemotherapy, such as doxorubicin, may preclude some patients from this second-line therapy. One retrospective study reported a male patient previously treated with 450 mg/m^2 doxorubicin who suffered cardiogenic shock and multiorgan failure during subsequent sunitinib treatment.[4] A study investigating the cytotoxicity of sunitinib using harvested left ventricular myocytes from rats found no evidence of cardioprotection with dexrazoxane treatment, suggesting that oxidative stress, though a critical mechanism of doxorubicin cardiotoxicity, may not be a significant cardiotoxic mechanism of sunitinib.[19]

Beyond these reports, the authors are unaware of any studies investigating the relationship between the cardiotoxicity of doxorubicin and that of sunitinib. Although the cumulative cardiotoxicity of doxorubicin may have predisposed the patient to CHF, it appears that it was secondary to sunitinib treatment rather than doxorubicin treatment. Further research regarding the cardiotoxic interaction of these 2 drugs is warranted.

Few reports exist that describe toxicities as a result of long-term interferon-α administration, and the authors are unaware of any study reporting long-term effects of low-dose interferon-α. A case report published in 2006 describes a patient being treated with 9 MU pegylated interferon 3 times a week who was tolerating treatment "relatively well" even after 4 years of therapy.[20] Side effects of low-dose interferon-α experienced by our patient include grade 1 anemia, grade 1 neutropenia, hand-foot syndrome, arthralgias, myalgias, and fatigue. Otherwise, no significant toxicities have arisen.

Conclusion

We report a patient with rapidly progressive metastatic sarcomatoid RCC refractory to doxorubicin and gemcitabine. The patient has had an apparent complete clinical response to sunitinib and low-dose interferon-α, which may represent a novel second-line treatment for this rare and aggressive tumor. Care must be taken to avoid cardiotoxicity associated with sunitinib administration, and close monitoring of LVEF percent with titration to a tolerable dose is recommended. This patient also illustrates the necessity for a multimodality approach to the treatment of sarcomatoid RCC.

Acknowledgments

The authors would like to acknowledge the patient for his strength of spirit and willingness to report on his progress.

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Review

Therapy for Kidney Cancer With a Sarcomatoid Component

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Sarcomatoid Renal Cell Carcinoma in the Context of Other Kidney Cancers

Metastatic kidney cancers have significant heterogeneity of biologic behavior, even within the approximately 75% that are clear cell type. An identifiable sarcomatoid component can be associated with rapid growth and a clinically aggressive course,[1] as in Fuhrman grade IV, which denotes bizarre, multilobed nuclei and heavy chromatin clumps.[2] The sarcomatoid category, defined by its appearance, may be a common endpoint of malignant evolution, further complicating comparison across cases that might have originated in different cell types. Because there are relatively few patients with sarcomatoid content, and most have a short survival, the process of testing new drugs and treatment algorithms is naturally more challenging than for other histologically-defined subsets. This low incidence makes case reports of positive outcomes and smaller series relatively more important in the process of seeking better approaches in general and for the development of a treatment plan for individual patients.

Bradshaw and colleagues[3] describe a case of sarcomatoid renal cell carcinoma in a 51-year-old man, which is notable for several clinical and pathologic findings. The nephrectomy specimen showed that the proportion of sarcomatoid differentiation was low, at 5%, but was present in a high-grade background. There was evidence of metastatic disease in the lungs and mediastinum; durable regression of metastasis following nephrectomy is a well known, but rare, event.[4] A brief period of observation verified that this patient was not in remission, as progression was noted several months after nephrectomy. On the other hand, experience with overall survival improvement attributable to nephrectomy in the setting of metastatic disease in otherwise operable, good-performance patients represents an early, concretely defined therapeutic maneuver with observable impact on median overall survival—an impact predating the targeted drug era by several years.[5] Contemporary discussion of an integration of this in the targeted drug era has been acknowledged.[6] The mechanisms of nephrectomy-induced regression of metastasis or of overall survival impact remain undefined. Certainly, quantitative or qualitative changes of cytokines emanating from the tumor bulk and shifts in the balance of immune tolerance versus immune attack are leading considerations.

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Development of a Therapeutic Plan

Instructively, the duration of remission in the patient was short, with only 2 months until multiple sites of disease appeared. The close interval radiologic and symptomatic assessments were key for timely initiation of medical therapy. One site was in the humerus, which may not be under routine surveillance. Bone lesions of kidney cancer may be purely lytic, and hard to discern on a bone scan.

Goals of therapy can be canonically considered to be life prolongation and amelioration of symptoms. In the patient, the first post-nephrectomy therapy comprised local therapy modalities: radiation and cryotherapy to symptomatic areas. Turning to medical anticancer treatments, the trials of targeted drugs such as sunitinib (Sutent, Pfizer), sorafenib (Nexavar, Bayer), everolimus (Afinitor, Novartis), interferon-α, and bevacizumab (Avastin, Genentech), which required a clear cell "component,"[7-11] undoubtedly had some patients with a sarcomatoid component. Data from a temsirolimus trial[12] also had similar patients, though the study did not have this histology restriction, but was certainly underpowered, if considering a specific impact on this small, sarcomatoid-containing subset. The first medical treatment administered to the patient, a doxorubicin and gemcitabine regimen, is notable for its 2 conventional cytotoxic drugs—a medical category eschewed for most clear cell kidney cancer treatment approaches because of low activity.[13] The reason for the relative sensitivity to conventional cytotoxics is not known, but could be attributed to a rapid growth. At the point of the patient's progression, the main objective was to find, with a rational basis, a therapy that could help.

The authors comment that "sunitinib has greater clinical efficacy than sorafenib," but cite a trial in which nobody was treated with sorafenib. Subsequent to this patient's treatment, there is now a trial directly comparing sunitinib followed by sorafenib versus sorafenib followed by sunitinib (NCT00732914); results are not yet avail-

able. Sunitinib and sorafenib are only 2 of 6 targeted drugs with activity in advanced kidney cancer currently on the market, each approved in trials with zero or very few subjects who had received prior therapy with the doxorubicin/gemcitabine combination. A separate issue from relative clinical activity is the comparison of the theoretical targets of sunitinib and sorafenib. These can be contrasted, referring to the manufacturer's prescribing information, with vascular endothelial growth factor receptor (VEGFR1 VEGFR2, VEGFR3), KIT, FLT-3, RET, and platelet-derived growth factor (PDGFR)-β listed for both; colony stimulating factor 1 receptor and PDGFR-α listed for sunitinib; and BRAF, CRAF, and mutant BRAF listed for sorafenib. The activity in kidney cancer may be attributable to blockage of VEGFR2 on the endothelial cells, in contrast to tumor cells themselves.[14]

None of these data, in particular the projected comparison of 2 of the available drugs, would have empirically informed an oncologist on the appropriate treatment plan for an individual patient presenting with sarcomatoid kidney cancer. The patient was started on a sunitinib plus interferon combination treatment, using 2 active agents, both with complex and only partly understood anticancer mechanisms. This combination has since been the subject of a single-arm trial, which reported a partial response rate of 12% and stable disease rate of 80% in the 25 treated subjects. The conclusion was that the regimen was of limited general promise, with 88% of patients having treatment interruptions.[15]

Ongoing stabilization and survival has been achieved in the patient by applying a maintenance interferon-α regimen. Although interferon represents the inferior group experience in the direct comparisons of sunitinib versus interferon,[7] temsirolimus versus interferon,[12] and combination bevacizumab plus interferon versus interferon alone,[10,11] there have been known major responses and low incidence of complete responses isolated over decades of interferon treatment of kidney cancer. Indeed, that limited but occasionally positive outcome was part of the basis for selection of interferon as a reference arm in many kidney cancer clinical investigations. The mathematically consistent observation that a given treatment may only seem to "benefit a few months" for the median outcome in a group in no way disputes that a benefit for a few outliers may be real and markedly out of proportion to the "average case."

Management of Toxicity

In an unusual collision of side effect profiles of drugs with markedly different mechanisms, both doxorubicin and sunitinib are associated with congestive heart failure (CHF). Doxorubicin-induced heart failure is well-studied, with proposed mechanisms including formation of free radicals, interaction with proteasomes, and lipid peroxidation.[16] In a large series,[17] cardiac failure was detected in less than 10% of patients who received a cumulative dose of doxorubicin that was higher than the one given to the patient described in the case study; few of those cases would have been as severe as the 10–15% ejection fraction seen in this case report. Features of sunitinib-associated CHF that contrast with anthracycline-induced CHF are that it is often reversible and may not be cumulative-dose associated, though the mechanism is not well characterized.[18] The clinical course of severe, established anthracycline-induced cardiomyopathy is typically not reversible, but fortunately, in this case, symptomatic failure was reversed after sunitinib was discontinued and interferon-α treatment was maintained.

Future Development

Bradshaw and colleagues present a patient who had good clinical outcome despite the presence of initial histologic high-risk features, rapid and multifocal progression, and short durability of first-line treatment. The authors and treating physicians are commended for innovation and perseverance, integrating diverse drugs (cytotoxics, immunotherapy, and kinase inhibitors) with multidisciplinary management comprising urologic surgery (nephrectomy), interventional radiology (cryotherapy), radiation oncology, and orthopedic surgery (humerus). Ironically, the last drug administered to the patient was also the one that has been used the longest for kidney cancer treatment. The future of kidney cancer therapy will grow in complexity, as more targeted drugs and combinations of drugs become available both in clinical trials and commercially. Each approach can be anticipated to have subtle or distinct differences in pharmacokinetics and targets that may be critical for individually selected cases. The challenge, which we expect to overcome with the application of basic advances, will be to understand the mechanisms driving the malignant behavior of the sarcomatoid kidney cancer phenotype. The message is clear: there may be opportunities to decode the significant biologic heterogeneity of kidney cancer. We hope to see improved outcomes, like that seen in this case, become the standard in this disease.

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