Case Report

Curability of Poor-Risk Metastatic Sarcomatoid Renal Cell Carcinoma with the Combination of Gemcitabine, 5-Fluorouracil, and Interferon-Alfa: A Case Report of a 55-Year-Old Man with a 10-Year Complete Remission

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Clinical Practice Points

- Sarcomatoid renal cell carcinoma(SRCC) is an aggressive malignancy and carries a poor prognosis.
- Cytotoxic chemotherapy or biochemotherapy should be considered as treatment options for SRCC.
- Durable remissions are achievable in SRCC with non-targeted therapy.

Clinical Genitourinary Cancer, Vol. xx, No. x, xxx
Keywords: Biochemotherapy, 5-Fluorouracil, Gemcitabine, Interferon-alfa, Metastatic Carcinoma, Sarcomatoid Renal Cell carcinoma

Introduction

Renal cell carcinoma (RCC) is the most common malignancy of the kidney, with about 4% of patients having sarcomatoid dedifferentiation. Sarcomatoid features can develop in conjunction with all subtypes of RCC, including clear cell renal carcinoma (8%), papillary renal carcinoma (3%), chromophobe renal carcinoma (9%), and collecting duct carcinoma (29%).[1] As a morphologic diagnosis, sarcomatoid renal cell carcinoma (SRCC) is defined by the spindled morphologic features of cells, resembling a sarcoma, among a background of the primary histologic renal carcinoma type. Despite the spindled appearance, SRCC does not routinely express mesenchymal markers,[2] so epithelial-mesenchymal transition has been proposed as a mechanism for SRCC evolution.[3] Regardless of the percentage of sarcomatoid cells present in the tumor, sarcomatoid dedifferentiation has been associated with a significantly worse prognosis independent of primary tumor grade or TNM stage.[4] Moreover, SRCC tends to present at an advanced stage.

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Submitted: Oct 22, 2012; Revised: Dec 22, 2012; Accepted: Apr 2, 2013

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Case Report

In 2002, A 55-year-old man with well-controlled adult-onset diabetes mellitus presented with a 4-month history of drenching night sweats, fever, and an unintentional 50-lb weight loss. A computed tomographic scan of the abdomen demonstrated a 6-cm left renal mass, a biopsy of which confirmed SRCC. A computed tomographic scan of the chest did not reveal any metastatic disease. The patient underwent an open left radical nephrectomy and lymphadenectomy in May 2002, with pathologic examination showing predominant sarcomatoid dedifferentiation, with a focal conventional (clear cell) component. Postoperatively, he continued to have constitutional symptoms and experienced refractory symptomatic anemia, requiring weekly transfusions of 2 units of packed red blood cells. One month postoperatively, a chest radiograph showed multiple nodules at the lung bases, and a technetium-99 bone scan showed an abnormal uptake suggesting metastasis to the right trochanter. Plain films confirmed the presence of an osteolytic lesion in the right femur, and a biopsy confirmed the presence of metastatic carcinoma. Restaging computed tomographic scans of the chest and abdomen showed local recurrence in the left renal fossa and metastasis to the contralateral kidney, as well as supradiaphragmatic and infradiaphragmatic adenopathy (Figure 1).

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2013.04.005

Figure 1 Postsurgical Restaging Computed Tomographic Scans of the Chest and Abdomen. (A) Note the Extensive Mediastinal Lymphadenopathy. (B) Note the bulky Retroperitoneal Lymphadenopathy

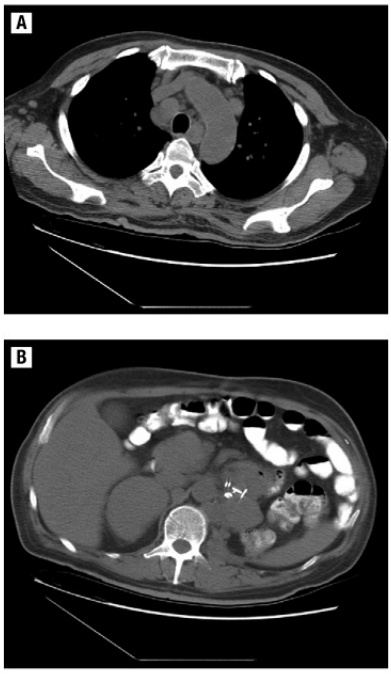
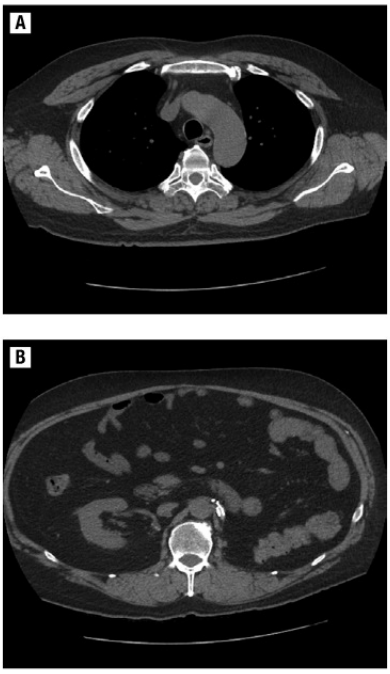


Figure 2 Computed Tomographic Scans Taken in 2012 of the Chest and Abdomen, showing complete response to therapy. (A) Corresponding Computed Tomographic Scan of the Chest Demonstrating Complete Resolution of Previous Lymphadenopathy. (B) Corresponding Computed Tomographic Scan of the Abdomen Demonstrating no Evaluable Disease



At presentation to M. D. Anderson Cancer Center, his Karnofsky performance status (KPS) was 30%. Laboratory investigations were significant for a hemoglobin value of 7.9 g/dL, a normal serum lactate dehydrogenase level (558 IU/L, with upper limit of normal of 618 IU/L), and a serum creatinine level of 1.8 mg/dL. The serum calcium level was 8.2 mg/dL, with a serum albumin level of 3.1 g/dL. After his KPS improved to 60% with best supportive care, systemic therapy was initiated with interferon (INF)-alfa one-half million units subcutaneously twice daily, 5-fluorouracil 150 mg/m^2/d (total daily dose 250 mg) administered by continuous infusion on days 1 to 21, and gemcitabine 200 mg/m^2 intravenously on days 1, 8, and 15 of a 28-day cycle.

After 2 cycles of this biochemotherapy regimen, the patient achieved a partial response in the renal fossa and supradiaphragmatic and infradiaphragmatic lymph nodes, with almost complete resolution of the bulky abdominal adenopathy. Biochemotherapy was then withheld, and radiation therapy was given to the right femoral lesion but was complicated by lymphedema and cellulitis, requiring 4 separate hospital admissions for intravenous antibiotics and hydration for acute kidney injury, with the serum creatinine concentration reaching 6.2 mg/dL. The patient never underwent dialysis but did require sevelamer for hyperphosphatemia, calcitriol for advanced kidney disease, and chronic epoetin for anemia.

His kidney function eventually improved; his most recent serum creatinine concentration was 2.16 mg/dL. The patient received a total of 8 cycles of biochemotherapy. In 2005, he had a fracture of the right hip requiring bipolar arthroplasty. The patient is currently followed yearly. He was last seen in clinic in February 2012 with a KPS of 80% and no evidence of tumor recurrence (Figure 2).

Discussion

Renal cell carcinoma (RCC) is the most common malignancy of the kidney, with about 4% of patients having sarcomatoid dedifferentiation. Sarcomatoid features can develop in conjunction with all subtypes of RCC, including clear cell renal carcinoma (8%), papillary renal carcinoma (3%), chromophobe renal carcinoma (9%), and collecting duct carcinoma (29%).[1] As a morphologic diagnosis, SRCC is defined by the spindled morphologic features of cells, resembling a sarcoma, among a background of the primary histologic renal carcinoma type. Despite the

spindled appearance, SRCC does not routinely express mesenchymal markers,[2] so epithelial-mesenchymal transition has been proposed as a mechanism for SRCC evolution.[3] Regardless of the percentage of sarcomatoid cells present in the tumor, sarcomatoid dedifferentiation has been associated with a significantly worse prognosis independent of primary tumor grade or TNM stage.[4] Moreover, SRCC tends to present at an advanced stage.

Reflecting the aggressive nature of SRCC, standard therapeutics are not as effective in SRCC as in RCC without sarcomatoid features. Unlike conventional-type RCC, patients with metastatic SRCC may not benefit from cytoreductive nephrectomy, and surgery may result in the decreased use of systemic therapy in these patients.[5] Unfortunately, although patients with SRCC were not excluded from the pivotal trials of anti–vascular endothelial growth factor agents or mammalian target of rapamycin inhibitors, sarcomatoid dedifferentiation was not a component of stratification nor was it reported.[6] In a retrospective review, 19% of patients with SRCC treated with anti–vascular endothelial growth factor therapy achieved a partial response,[7] but none achieved a complete response to therapy.

Experience with immunotherapy, chemotherapy, or combination biochemotherapy has been variable in SRCC. Based on retrospective data, response rates to interleukin-2– and INF-alfa–based regimens may be as high as 33%.[8] Although INF may produce responses, tolerability may limit its utility, especially when combined with other agents. Low-dose INF appears to have efficacy comparable to that of intermediate-dose INF, with a lower incidence of grade 3 and grade 4 adverse events, including lower rates of depression, resulting in improved quality of life.[9] Fluoropyrimidine-based regimens may produce superior response rates compared with other treatments.

Prospectively, only doxorubicin 50 mg/m^2 on day 1 with ifosfamide 2500 mg/m^2 with mesna on days 1 and 2 of 21-day cycles, and doxorubicin 50 mg/m^2 on day 1 with gemcitabine 1500 mg/m^2 on day 1 of 14-day cycles, have been studied in SRCC.[10,11] In these 2 clinical trials, the response rates were 0% and 16%, respectively, with 1 patient treated with doxorubicin and gemcitabine achieving a complete response. The combination of a fluoropyrimidine, either 5-fluorouracil or capecitabine, and gemcitabine has been studied prospectively in conventional-type RCC in 4 phase II clinical trials[6] but not in SRCC. Response rates range from 8% to 17%, with continuous-infusion 5-fluorouracil producing the best results. Since SRCC is more virulent than conventional-type RCC, such cytotoxic chemotherapy regimens may have greater efficacy in this subgroup of patients.

Our patient represents evidence for such an improved effect, but what role each component of this patient's therapy played in producing the response and cure is unclear. The combination of doxorubicin 50 mg/m^2 and gemcitabine 1500 mg/m^2 was also reported to produce 2 long-term remissions,[12] suggesting that gemcitabine is an important contributor given the lack of efficacy demonstrated with the combination of doxorubicin and ifosfamide. The regimen of capecitabine 1650 mg/m^2 on days 1 to 21 and gemcitabine 1000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle has demonstrated only modest clinical activity in the phase II setting after targeted therapy[13] but has been reported to produce remissions.[14] However, our patient received reduced-dose chemotherapy, suggesting that INF may have had a significant synergistic effect in his favorable outcome. Combining INF with cytotoxic chemotherapy has not been shown to increase efficacy of chemotherapy in clinical trials, but low-dose INF was not used. It has been postulated that the primary effect of INF on RCC may be antiangiogenic,[15] and one could hypothesize that twice daily low-dose INF would have a similar, or even more potent, antiangiogenic effect compared with intermediate-dose INF, with improved tolerability.

Long-term survivors of SRCC have been reported.[16-19] Successful regimens have included doxorubicin with gemcitabine or ifosfamide, 5-fluorouracil–based biochemotherapy, and sunitinib with low-dose IFN. It is difficult to tease out the exact contributions of each therapeutic component, but in reconciling past experiences with our case it appears as though the specific chemotherapy agents may not be as important as delivering a tolerable treatment program with any of the agents mentioned. This may help to explain why the addition of low-dose IFN helps in producing long-term survivors, increasing antitumor effect without significantly worsening toxicity. This is especially true in our patient, given his poor performance status at presentation.

Conclusion

Although targeted therapy represents standard of care for conventional-type RCC, to date no long-term remissions of SRCC have been reported with targeted therapy. We report a patient with SRCC and poor-risk features, including a low KPS, who had a complete response to low-dose INF, infusional 5-fluorouracil, and gemcitabine, and whose response has been remarkably durable over 10 years. Such experience should lead us to reexamine the role of chemotherapy or biochemotherapy in the treatment of patients with RCC in the context of a randomized trial. Ideally, future trials would be guided by the genetic signatures or biomarkers of such highly responsive tumors, but in their absence, empirical studies incorporating low-dose INF with chemotherapy seem warranted. For patients with SRCC, our experience with this case suggests that cytotoxic chemotherapy or biochemotherapy combinations should be strongly considered.

Disclosure

The authors have stated that they have no conflicts of interest.

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