Clinical and Pathological Complete Remission in a Patient With Metastatic Renal Cell Carcinoma (mRCC) Treated With Sunitinib: Is mRCC Curable With Targeted Therapy?

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A B S T R A C T

We report a patient with metastatic clear-cell renal cell carcinoma (mRCC) who presented with primary tumor in situ in the left kidney and metastases to bone, liver, lungs, and brain. After over 5 years of sunitinib therapy and subsequent cytoreductive left nephrectomy, the patient achieved radiographic complete response (CR) and had pathologic CR in the nephrectomy specimen. Durable clinical and pathological CRs are possible with targeted agents, even with primary tumor in situ and widely disseminated metastases. Ongoing research will define the optimal duration of systemic therapy in exceptional responders and identify the molecular determinants of response and resistance.

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Introduction

Targeted agents including multi-tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of metastatic renal cell carcinoma (mRCC) and have supplanted cytokine therapy as the standard of care in clinical practice. While targeted therapies have significantly improved patient outcome in terms of progression-free survival and overall survival, most patients achieve stable disease or a partial response; the complete remission (CR) rate is much lower and has been reported to be about 3% with sunitinib in a phase III trial.1 CRs have primarily been described in case reports/series, with the majority of patients receiving sunitinib, with or without surgical intervention.2 CR has been noted in many different metastatic sites, including adrenal, hepatic, and pancreatic metastases, with decrease in pulmonary metastases being the most common; CR of brain metastases has been much less commonly reported.3 We report here a case of a clinical and a pathological CR after treatment with sunitinib in a patient who presented with primary RCC in situ in the left kidney and widely metastatic disease.

Case presentation

A 46-year-old Caucasian male patient presented in March 2006 with left flank pain, micro-hematuria, and a 15-pound weight loss. A CT scan of the abdomen demonstrated a 10-cm heterogenous enhancing mass involving the upper pole of the left kidney. A biopsy of the renal mass confirmed the presence of Fuhrman nuclear grade 3 clear-cell RCC. The remainder of body imaging demonstrated multiple sub-centimeter lung nodules, mediastinal adenopathy, and femoral and vertebral lytic lesions. Given that the patient was neurologically intact, it was decided to defer whole brain radiation and start systemic therapy with sorafenib 400 mg twice daily.

At the 16-week restaging visit, the patient was found to have progression of the primary tumor, multiple new lytic osseous metastases, increase in number and size of pulmonary metastases, and interval development of new bilobar hepatic metastases. At that time (August 2006), sorafenib was discontinued and sunitinib was started at 50 mg daily for 28 days on and 14 days off. At his 6-week restaging visit from initiation of sunitinib, patient’s disease responded in the liver and lungs. At the 24-week restaging visit, there was noted improvement in the size of the brain metastases, which then resolved entirely by the 30-week restaging visit. After five and half years of sunitinib therapy, the patient developed new-onset hypertension and was hospitalized because of hypertensive crisis. Sunitinib therapy was therefore discontinued (February 2012). Given these adverse events and the achievement of a clinical and radiographic CR in all metastatic sites (Figs. 1-3), a multidisciplinary decision was made for the patient to undergo a cytoreductive
Figure 1. T1-weighted contrast-enhanced MRI of the brain: Pre-treatment scan shows an enhancing metastasis with surrounding edema. After systemic treatment, a tiny residual lesion is visible, consistent with scarring.

Figure 2. Contrast-enhanced CT of the abdomen: Pre-treatment scan shows a large heterogeneously enhancing, partly calcified, primary mass in the left kidney. Post-treatment study shows a smaller, homogenously hypodense lesion with calcific rim, suggestive of treatment changes. Ultimately, a nephrectomy was undertaken; on pathology, this mass showed only necrosis and no active disease.

Figure 3. CT of the pelvis with bone windows: Pre-treatment scan shows a lytic lesion in S1 vertebral body and small lesion in the right iliac bone. Post-treatment scans show a smaller S1 lesion, not actively lytic, with a sclerotic rim, suggestive of no active disease. The right iliac lesion is no longer evident.
left nephrectomy. In May 2012, the patient underwent a laparoscopic left radical nephrectomy; pathology review of the left kidney showed necrosis with no viable tumor seen, and negative resection margins. The patient has been off systemic therapy for close to 3 years and remains without evidence of disease as of December 2014.

Discussion

There have been few reports in the literature of brain metastases responding completely to sunitinib in the absence of radiotherapy or surgical resection. Lim et al performed a retrospective study of six patients, each with more than two brain metastases, and found a near CR in three patients with sunitinib therapy alone; patients with supratentorial, asymptomatic, small metastases with no associated hemorrhage were good candidates to receive upfront systemic therapy. An open-label expanded access trial of sunitinib evaluated 4371 patients, 7% of whom (321 patients) had baseline brain metastases; the general safety profile and tolerability of sunitinib was comparable between patients with brain metastases and the general mRCC population, but outcomes were significantly worse for the brain metastases group. Further data is needed regarding the optimal duration of systemic therapy in exceptional responders to TKIs, and who among these responders will remain in remission after discontinuation of therapy. Research is ongoing to characterize the molecular determinants of response and resistance to targeted therapy.

Conclusion

TKIs have revolutionized the treatment of mRCC. While response rates to first-line TKI therapies are approximately 30%, most patients ultimately develop progressive disease and succumb to their cancer. We report here a patient with clear-cell RCC who had metastases to bone, liver, lungs, and brain, and achieved a complete clinical and pathological response to sunitinib. The patient continues to be disease-free close to 3 years after discontinuation of therapy. To our knowledge, this is the first report of a patient with both a dramatic complete resolution of multiple brain metastases with TKI therapy and pathological CR of primary renal tumor, suggesting cure with TKIs alone is possible.

Conflict of interest statement

Jose A. Karam has acted as a one-time consultant for Pfizer. Nizar M. Tannir has disclosures (research funding and honoraria for participating in advisory boards and lectureships).

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