**CASE STUDY**

**65-YEAR-OLD MALE WITH RENAL CELL CARCINOMA AND LUNG METASTASES**

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**BACKGROUND**

A 65-year-old male with superior physiologic appearance presented to his family physician for routine checkup. His medical history, social history, and family history were all unremarkable, and he had no significant complaints. Baseline laboratory data were within normal limits. However, his physician noted a left upper quadrant mass. Upon further studies, abdominal computed tomography (CT) scan discovered a 10-cm right renal mass. CT scan of the chest demonstrated enlargement of the mediastinal and hilar lymph nodes, as well as scattered pulmonary nodules, the largest approaching 2 cm. Bone scan results were negative. Bronchoscopy and transbronchial needle biopsy identified lung malignancy, and CT-guided biopsy of the renal mass revealed histologic findings compatible with clear cell renal cell carcinoma (RCC).

(Continued below)

Which of the following do you recommend: cytoreductive nephrectomy (CN), high-dose interleukin-2 (IL-2), sunitinib, sorafenib, temsirolimus, bevacizumab ± interferon α (IFNα), gemcitabine + capecitabine, or investigational therapy?

**Dr Jonasch:** Because this patient appears to have most of the disease in his primary tumor, with a relatively small amount of systemic disease and a resectable renal mass, CN followed by cytokine (immunotherapy) therapy would be a reasonable choice. It is not clear whether CN would provide any additional benefit if this patient was treated with targeted therapy.

**Dr Pili:** At my facility, our general approach is laparoscopic CN to shorten recovery and to reduce length to initiation of systemic therapy. Tumor burden, especially with implicated symptoms and absence of extensive systemic disease, guide the decision to perform CN.

**Dr Hutson:** When choosing to perform CN, the patient must be surgically fit, and the tumor must be surgically operable, with some consideration given to tumor volume.

**Dr Jonasch:** Performance status of the patient should be considered, but is not always significantly improved post-CN. CN before cytokine therapy seems to show benefit regardless of performance status, site of metastases, and the presence of measurable disease (Southwest Oncology Group 8949 and European Organization for Research and Treatment of Cancer 30947 clinical trials), although this benefit is of significantly greater magnitude in patients with good performance status and lung-only disease. We generally will not perform up-front resection of patients with poor performance status or extensive metastatic disease. It is not clear if this applies to targeted therapies.

**Dr Pili:** High-dose IL-2 is most beneficial in patients who have the highest probability of response and who have had a major debulking of their disease.

**Dr Jonasch:** I agree that the patient will probably not respond to immunotherapy unless clear cell features predominate. There are emerging data suggesting that targeted therapies are the agents of choice for non-clear cell histologies, particularly temsirolimus for papillary RCC.

**Dr Jonasch:** In summary, CN is not appropriate for all patients and should be based on physician experience and on a case-by-case basis. With the newer targeted agents, CN does not appear to be necessary to enhance response to therapy. The role of high-dose IL-2 remains to be debated and may be appropriate in selected patients.

**Dr Pili:** Can you comment about your facility’s criteria for total versus partial nephrectomy?

**Dr Jonasch:** It is based on the urologist’s surgical skill, which is probably the same criterion used in many other facilities.

**Dr Jonasch:** It is a fairly complex algorithm that takes into consideration other criteria, such as central tumor, multifocality, and surgical history. We also have to determine how much of the renal parenchyma is safe and reasonable to remove.
Dr Pili: I agree, and tumor location is also important. The criterion for total nephrectomy is usually a tumor size of 4 to 7 cm or greater. However, partial nephrectomy is preferred over total nephrectomy to avoid future renal insufficiency and dialysis requirements.

The patient was referred for open nephrectomy, in which a 10.5-cm tumor was removed (class T4: invasion into regional lymph nodes and the surrounding kidney envelope called the Gerota’s fascia). Pathology reported Fuhrman Nuclear Grade III cancer cells with focal areas of sarcomatoid differentiation and confirmed the RCC type as conventional (or clear cell). The patient was referred to an academic oncology clinic for systemic treatment of metastatic RCC. At the time of clinic presentation, he was asymptomatic with good performance status (Eastern Cooperative Oncology Group performance status = 0 and Karnofsky’s index of performance status = 90). Chest CT scan confirmed an increase in lymph node enlargement. Abdominal CT scan revealed a 3-cm left retroperitoneal (RP) lymph node, an indication of regional metastasis. Brain magnetic resonance image and bone scan showed no evidence of metastasis, which remained consistent throughout the course of this discussion. Serum creatinine was slightly elevated (as expected postnephrectomy), whereas remaining laboratory values were within acceptable limits. CN was performed. What would be the next therapeutic option?

Dr Jonasch: This patient has good performance status and does not appear to meet the criteria for poor risk as defined by the temsirolimus study. (Common risk factors associated with shorter survival include metastasis within 1 year of diagnosis, metastases in multiple organs, poor performance status, anemia, and elevated serum lactate dehydrogenase [LDH] and calcium.6) However, the presence of sarcomatoid cells and high-grade cell histology is associated with poorer prognosis.7 These features and the presence of intra-abdominal adenopathy, which is unconfirmed in this patient, is associated with failure to high-dose IL-2.4 Temsirolimus would not be my first choice either, because patients with clear cell histology seem to derive less benefit from this agent.6 Bevacizumab ± IFNα is not approved by the US Food and Drug Administration for this indication to date but could be a promising option. Sorafenib as compared to other agents does not appear to demonstrate as much benefit in the front-line setting. My choice for systemic therapy would be sunitinib or investigational therapy.

Dr Pili: Because sarcomatoid features are a morphological classification subject to limitations, it is unclear if its presence is an indicator of poor response to high-dose IL-2. Observation is a reasonable decision for some small, slow-growing renal masses, even if high-grade tumors exist. However, this choice is typically reserved for elderly patients, particularly with significant comorbidities, or if metastasis is absent or at low risk. It should be noted that a delay in systemic therapy for larger, aggressive tumors should be avoided, because tumor burden seems to affect therapy response.

Dr Hutson: Because of the variable natural history of RCC in individuals, it is not uncommon for patients to be in the observation mode, especially for small-volume disease. Based on treatment algorithms and published phase III trials, an option for first-line therapy could be sunitinib for patients with good-to-intermediate risk factors, which would be my choice for this patient.5 Bevacizumab ± IFNα would be an attractive alternate. High-dose IL-2 would be an option for a select group of patients; however, results of a pivotal clinical trial are still pending.

The patient was enrolled in the treatment arm of a randomized phase II clinical trial of sorafenib 400 mg twice daily versus IFNα. After 12 months of therapy, he remained minimally symptomatic with no change in his performance status. However, chest CT scan showed progressive disease. Abdominal CT scan found no liver lesions, but the left RP lymph node had increased to 5.7 cm. Despite disease progression, a favorable central necrosis was noted in the RP lymph node soft tissue mass, an effect seen with antiangiogenic therapy. Moderate-to-severe adverse effects were reported, but they were acceptable to the patient. Although laboratory values remained within acceptable limits, serum calcium (11 mg/dL) and LDH (190 U/L) were now elevated from baseline. The patient desires additional therapy.

Dr Pili: Investigational therapy or changing to an anti-vascular endothelial growth factor therapy (bevacizumab ± IFNα) to combat induced resistance would be reasonable options. Sorafenib dose escalation would also be reasonable, because a recent phase II trial showed that sorafenib dose escalations up to 1600 mg per day produced antitumor activity in tolerant patients with metastatic RCC.10 However, refractory disease may not respond to dose escalation, thus I would be more apt to change to sunitinib based on recent American Society of Clinical Oncology data that suggested lack of cross resistance between sorafenib and sunitinib.11

Dr Jonasch: Would you comment further on the definition of disease progression and dose escalation versus changing to agents with alternate mechanisms of action (mTOR inhibitors)?

Dr Jonasch: It is not clear if disease progression differs between patients on immunotherapy versus targeted therapy. However, if a patient is tolerating a drug with limited, nonthreatening pulmonary nodules without new organ involvement, continuing therapy or dose escalation could be reasonable options. Switching to IL-2 after sorafenib therapy may not be appropriate because of potential additive cardiotoxicity associated with these agents individually.12,13 Gemcitabine plus capecitabine has demonstrated an objective response in studies.14 However, toxicities associated with this combination require vigilant patient selection and dosage adjustments. My choice for this patient would be investigational therapy or sunitinib.

As per trial protocol, dose escalation to sorafenib 600 mg twice daily was per-
mitted. Nine months after dose escalation, CT scans discovered new lesions in the chest and abdomen, as well as an increase in the size of the pulmonary and mediastinal lymph nodes. No new sites of disease metastasis were found, and serum calcium and LDH remained elevated. Because he remained asymptomatic with good performance status, the patient elected to receive further therapy.

Dr Jonasch: In order for dose escalation to be permitted, it appears that the toxicities improved in this patient, an occurrence that has been observed in patients receiving TKIs.

With continual dosing, tolerance to the side effects of targeted agents can develop, particularly with sorafenib because it does not require a treatment break.

Systemic therapy was changed to axitinib 5 mg twice daily, an experimental agent. He experienced low-grade, manageable toxicities (diarrhea and hypertension). Because CT scans demonstrated an unconfirmed partial response, he is currently continuing on axitinib therapy.

Dr Hutson: Axitinib is a multitargeted TKI with a profile similar to that of the TKIs sunitinib and pazopanib. This approach is similar to what we have discussed as second-line therapy options for patients who have received sorafenib.10

REFERENCES