**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).

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 Hutson:** 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 Jonasch:** 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 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 complicated symptoms and absence of extensive systemic disease, guide the decision to perform CN.

**Dr Hutson:** Although data do seem to support CN for RCC, does the presence or absence of CN dictate your choice of systemic therapy?

**Dr Pili:** Although it is patient specific, high-dose IL-2 seems to show more benefit than IFNα.

**Dr Jonasch:** 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 Hutson:** Would histology influence one’s selection?

**Dr Pili:** The best data for response to immunotherapy are in patients with clear cell histology. It is unclear if immunotherapy will benefit mixed histology types of RCC. Tyrosine kinase inhibitors (TKI) and mammalian target of rapamycin (mTOR) inhibitors seem to show activity in clear cell and other types of RCC.

**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 my opinion, high-dose IL-2 is a good option for selected patients (including this particular case) in whom studies have demonstrated a complete response. Predictors of favorable response to IL-2 include prior CN, intermediate-to-good prognostic features, clear cell histology, and high carbonic anhydrase IX expression (commercially unavailable test for this case). Metastasis to a single organ, typically the lung, tends to be a predictor of response to cytokine therapy. However, targeted agents may be a more suitable option if the goal of therapy is to shrink the tumor.

**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 clinical 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 metastases, 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.) However, the presence of sarcomatoid cells and high-grade cell histology is associated with poorer prognosis. These features and the presence of intra-abdominal adenopathy, which is unconfirmed in this patient, are associated with failure to high-dose IL-2. Temsirolimus would not be my first choice either, because patients with clear cell histology seem to derive less benefit from this agent. 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. 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. 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.

**Dr Hutson:** Dr Jonasch, could 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. Gemcitabine plus capecitabine has demonstrated an objective response in studies. 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 permitted. 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 Janach: 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.

Dr Hutson: 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.

QUALITY-OF-LIFE CONSIDERATIONS FOR PATIENTS WITH RCC

Commentary provided by Sinibaldi VJ

Renal cell carcinoma tends to occur more commonly after age 55, in men and Hispanics, and in patients with familial disease.14 RCC is difficult to diagnose in the early stages of disease, because screening tests are unavailable, and signs and symptoms are generally not present initially.16 Once the tumor has grown or the cancer has spread, symptoms of RCC may include blood in the urine, abdominal mass, persistent unexplained fever, flank or lower back pain, fatigue, lower extremity edema, or rapid weight loss. Disease symptoms and drug adverse events may overlap to include pain, gastrointestinal changes, fatigue, depression, confusion, and hematologic changes.17

Because RCC is treated in the inpatient (ie, surgery) or outpatient (ie, systemic therapies at home or in a clinic) settings, nursing care should focus on overall patient well-being. Inpatients and outpatients require a multidisciplinary approach to maximize patient outcomes, enhance quality of life, and minimize drug toxicities. Often serving as primary patient liaisons, nurses are well positioned to assess response to care, evaluate adverse events associated with disease progression or systemic therapies, and educate patients concerning drug therapies and disease symptoms. Nurses can provide psychosocial support to patients and families by offering cancer coping principles and financial/reimbursement advice. In addition to indirect costs (eg, loss of wages) associated with RCC, direct costs of targeted therapies are high, amounting to as much as $100,000 annually.16 Limited financial assistance is available through some of the pharmaceutical companies depending on individual situations.

Hospital discharge planning should address postoperative wound assessment for complications, patient education about wound care and available systemic therapies, nutritional counseling, pain assessment, and follow-up care instructions.17 Follow-up appointments with their surgeon and medical oncologist are critical to assure that patients will have ongoing assessment of their recovery from surgery and disease status. The medical oncologist will be the important provider of systemic care. Nurses in outpatient settings have a critical role in monitoring patients for toxicities from the systemic treatments and symptoms of disease progression. In-depth assessments of physical and psychosocial concerns when patients present for interim laboratory tests or treatments aid in early identification of and intervention to promote symptom control and maintain or improve quality of life. Patients should be instructed to contact their oncologist or oncology nurse when disease symptoms or drug toxicities occur that may indicate a change in dose or therapy is required. Written information concerning drug side effects, interactions, dosing, and self-administration provides patients with tools to optimize therapy. Some useful Web site resources for this information may include:

- www.fda.gov/cder/drug/InfoSheets/patient/sorafenibPIS.htm
- www.fda.gov/cder/drug/InfoSheets/patient/sunitinibPIS.htm
- www.sutent.com
- www.nexavar.com

REFERENCES

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