Multidisciplinary Management of Advanced Kidney Cancer

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ABSTRACT

A number of therapeutic options are available for the treatment of advanced kidney cancer, including targeted therapy, immunotherapy, and nephrectomy. Choice of therapy for advanced kidney cancer is guided by risk stratification. Immunotherapy combinations are generally superior to vascular endothelial growth factor-based monotherapy, and overall survival rates continue to increase substantially. With new systemic therapy options, additional improvements have been noted in durable responses to treatment and in quality of life. Nephrectomy remains an important consideration in selected patients, particularly those with minimal burden of metastatic disease. Managing the adverse events of treatment of advanced kidney cancer requires close attention and multidisciplinary collaboration.

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At the NCCN 2020 Virtual Annual Conference, cases were presented to illustrate management of advanced kidney cancer.

Delayed or Immediate Nephrectomy?

The first case history was a 50 year-old man who had left shoulder pain and a mass in his arm. Imaging revealed multiple renal masses in the right kidney near the right renal vein and small masses in the left kidney.

His workup revealed no lung or brain metastases. Biopsy of the humerus confirmed that he had clear-cell renal cell carcinoma (RCC). He had radiation to the humerus. Levels of lactate dehydrogenase (LDH), creatinine, and hemoglobin were normal, but he had elevated serum calcium. His performance status was excellent.

“The question is, do we do a cytoreductive nephrectomy in this patient?” asked Chad A. LaGrange, MD, Chair of Urology, University of Nebraska Medical Center, who presented this case for consideration.

Some guidance is available from the randomized CARMENA trial, conducted at 79 centers with a total of 450 patients with metastatic RCC randomized to nephrectomy plus sunitinib versus sunitinib alone.¹ Patients were stratified according to risk factors, and more than 40% were poor risk. There were more patients at poor risk in the nephrectomy/sunitinib arm, and survival was lower in that arm of the trial. At a median follow-up of 50.9 months, sunitinib was noninferior to nephrectomy/sunitinib in patients with intermediate or poor risk clear-cell RCC, but not in patients with good risk.

“In fact, nephrectomy/sunitinib could be harmful in selected patients,” Dr. LaGrange said. “Why does

a urologist report a study showing you don’t need cytoreductive nephrectomy?” he asked. “Patient selection is the key.”

The group randomized to the nephrectomy arm had a higher rate of T3–T4 disease (70.1% vs 51% for sunitinib alone). Both arms also had significant patient attrition, and 38 patients had delayed nephrectomy at a median of 11 months from randomization.

“Median survival was only 18.4 months, which is inconsistent compared with other trials,” he said.

The SURTIME trial evaluated immediate nephrectomy followed by sunitinib versus deferred nephrectomy and sunitinib first in 99 patients with metastatic RCC.² There was no significant difference in overall survival, but survival numerically favored deferred nephrectomy.

“Therefore, selecting patients who are responders to systemic therapy is a good option,” he stated. “With delayed nephrectomy, more patients will get systemic therapy.”

The patient in the first case started treatment with axitinib. Follow-up CT scans showed a dramatic decrease in the right renal mass and decreases in size in the left renal masses. The patient underwent partial nephrectomy of the right kidney and cryoablation on the left renal mass. In 2014, the patient underwent cryoablation of another renal mass. In 2016, the patient underwent resection of solitary transverse colon mesentery mass and radiation to left front and right parietal lesion. Axitinib was restarted in June 2017, and nivolumab was started in March 2019. The patient had stable brain lesions, no new disease, and ECOG 1

performance status. As of this report, the patient is still alive.

Initial Treatment Options in Advanced Renal Cell Carcinoma

M. Dror Michaelson, MD, PhD, Associate Professor of Medicine, and Clinical Director, Genitourinary Cancer Center, Massachusetts General Hospital Cancer Center, presented 3 case reports describing initial treatment options in advanced RCC. The first case was a 61-year-old man with increasing back pain progressing to unsteady gait.

MRI revealed a mass at T5 with severe spinal canal stenosis, and the patient was admitted for urgent surgical decompression. Imaging revealed a 5-cm renal mass, “which is concerning for RCC,” he said, as well as indeterminate sub-centimeter lung nodules. His medical history was notable for hypertension and ongoing smoking.

Initial management entailed surgical decompression at T5, with full neurologic recovery. The patient then received adjuvant stereotactic body radiation therapy (18 Gy) to T4–T6. One month later, he had a radical nephrectomy with the following findings: 6 cm clear cell RCC invading perirenal fat; Fuhrman grade 3 or 4; no sarcomatoid features; pathologic stage, T3a; and negative surgical margins.

Tumor histology from the spine was identical to that from the primary renal mass. Chest CT showed minimal increase in bilateral lung nodules (2–5 mm).

Options for subsequent management include active surveillance; systemic therapy with VEGFR TKI monotherapy, combination therapy with CTLA4/PD-1, or combination therapy with VEGFR TKI/PD-1. Two recent phase III trials of frontline treatment of RCC provide some guidance for treatment selection.^{3,4}

CheckMate 214 compared ipilimumab/nivolumab versus sunitinib and showed an overall survival benefit for the immunotherapy combination in intermediate- and poor-risk patients with metastatic RCC.³ At 30 months, overall survival was 60% versus 47% for sunitinib in intermediate- and poor-risk patients, but no significant difference was seen between the 2 regimens in favorable-risk patients.

KEYNOTE-426 compared pembrolizumab/axitinib versus sunitinib and also showed an overall survival benefit for the immunotherapy combination in treatment-naïve patients with metastatic RCC: at 18 months, overall survival was 82.3% versus 72.1% for sunitinib.⁴

Other choices for initial therapy of advanced RCC include avelumab/axitinib, which is FDA-approved based on improved progression-free survival compared with sunitinib. In the JAVELIN Renal 101 trial, progression-free survival was 13.8 months for the

immunotherapy combination versus 8.4 months with sunitinib ($P<.001$).⁵

Atezolizumab/bevacizumab has also shown a progression-free survival benefit over sunitinib but this combination is not FDA approved at this time. Two different, highly promising regimens are also being studied in separate phase III trials versus sunitinib: pembrolizumab/lenvatinib and nivolumab/cabozantinib. These results have not yet been reported.

The current preferred recommendations for favorable-risk patients include axitinib/pembrolizumab, pazopanib, and sunitinib (Figure 1). Preferred regimens for poor- and intermediate-risk patients are ipilimumab/nivolumab (category 1), axitinib/pembrolizumab (category 1), and cabozantinib.

Preferred subsequent therapies include cabozantinib (category 1), nivolumab (category 1), or ipilimumab/nivolumab.

Back to the patient in case 1, who has been followed with active surveillance since spinal decompression and nephrectomy in May and June 2016, respectively. The patient continues to have slowly growing lung nodules and has developed an adrenal mass and contralateral renal mass. The latest MRI of the spine shows no evidence of disease.

The patient has no symptoms of disease, normal lab evaluations, and was working full-time until the COVID-19 pandemic.

Case 2 was of a 51-year-old man with gross hematuria seen in September 2018. Initial management at that time was nephrectomy. Pathology report revealed pT3a clear-cell RCC, Fuhrman grade 4, and no sarcomatoid or rhabdoid features. In March 2019, CT of the chest revealed an increase in lung nodules up to 15 mm. CT-guided lung biopsy in May 2019 was consistent with metastatic RCC. The patient's performance status was ECOG 0, and lab tests were normal.

Frontline treatment with axitinib/pembrolizumab was begun in June 2019. The patient's thyroid stimulating hormone level increased from 3.4 at baseline to 130, and treatment with levothyroxine was initiated. He had no other treatment-related adverse events.

The dose of axitinib was escalated to 7 mg twice a day in September 2019, and imaging the following January showed regression or resolution of all lung nodules and a mild increase in bilateral paratracheal and subcarinal nodes, measuring up to 8 mm from 4 mm previously. Of note, the increased adenopathy likely reflects an immune response, rather than increase in disease burden. The plan is to continue treatment for up to 2 years and then take a break.

Initial Treatment of Poor-Risk RCC

Case 3 is of a 64-year-old man who presented with gross hematuria, weight loss, and night sweats in January

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	Preferred regimens	Other recommended regimens	Useful under certain circumstances
Favorable ^a	<ul style="list-style-type: none"> • Axitinib + pembrolizumab • Pazopanib • Sunitinib 	<ul style="list-style-type: none"> • Ipilimumab + nivolumab • Cabozantinib (category 2B) • Axitinib + avelumab 	<ul style="list-style-type: none"> • Active surveillance^b • Axitinib (category 2B) • High-dose IL-2^c
Poor/intermediate ^a	<ul style="list-style-type: none"> • Ipilimumab + nivolumab (category 1) • Axitinib + pembrolizumab (category 1) • Cabozantinib 	<ul style="list-style-type: none"> • Pazopanib • Sunitinib • Axitinib + avelumab 	<ul style="list-style-type: none"> • Axitinib (category 2B) • High-dose IL-2^c • Temsirolimus^d
SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY			
Preferred regimens	Other recommended regimens	Useful under certain circumstances	
<ul style="list-style-type: none"> • Cabozantinib (category 1) • Nivolumab (category 1) • Ipilimumab + nivolumab 	<ul style="list-style-type: none"> • Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab (category 3) 	<ul style="list-style-type: none"> • Bevacizumab or biosimilar^e (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients^c (category 2B) • Temsirolimus^d (category 2B) 	

Figure 1. First-line and subsequent therapy for kidney cancer in the NCCN Guidelines for Kidney Cancer.⁶ © National Comprehensive Cancer Network, Inc 2020. All rights reserved. Accessed January 23, 2020. To view the most recent and complete version of the guideline, visit NCCN.org.

2018. In February, he underwent radical nephrectomy/thrombectomy. Pathology revealed pT4N0MO and Fuhrman Grade 3 clear cell RCC. In May 2018, the first surveillance scan showed multisite metastases (recurrent mass in the nephrectomy bed; new adrenal and bilobar hepatic metastases; and new pulmonary nodules). The patient had anorexia, and night sweats recurred. The bloodwork was significant for thrombocytosis (platelets >500,000 μ g).

From June to July 2018, the patient was treated with 4 cycles of ipilimumab/nivolumab. This was well tolerated, and he went on to receive nivolumab monotherapy monthly. Scans showed a near-complete response. In February 2019, he experienced a seizure in the waiting room, and imaging demonstrated interval development of brain metastases. He ultimately died of progressive central nervous system disease in January 2020.

Lessons from clinical trials show the long-term, “big picture” benefit achieved in patients with International Metastatic RCC Database Consortium intermediate- or poor-risk RCC receiving these new standard regimens. In CheckMate 214, nivolumab/ipilimumab showed significantly better 2-year overall survival versus sunitinib: 66% versus 53%, respectively ($P<.0001$).³ In KEYNOTE 426, axitinib/pembrolizumab versus sunitinib in 592 intermediate- and poor-risk patients had a median overall survival at 12 months of 86.7% versus 71.9% ($P=.00004$).⁴

“The outcomes are similar with both immunotherapies, with an early separation of curves for both immunotherapies, but follow-up is much longer for CheckMate 214. The durability of response is there for nivolumab/ipilimumab, but it is too early to tell for axitinib/pembrolizumab,” Dr. Michaelson continued. “We expect updated survival results from KEYNOTE-426 later in 2020.”

Immunotherapy combinations have a favorable adverse event profile compared with sunitinib. The toxicity data show ongoing quality of life benefit with the axitinib/pembrolizumab combination, although there is a greater need for toxicity-related treatment discontinuation and need for immunosuppression with nivolumab/ipilimumab.

In summary, Dr. Michaelson emphasized the following take-home messages:

- There are multiple good systemic therapy options for metastatic RCC, with no obvious clear choices in some cases.
- Good-risk patients and those with favorable intermediate risk can have survival of many years with and without therapy.
- Consider debulking nephrectomy and/or active surveillance in selected patients.
- Patients with Intermediate and/or poor risk generally require prompt initiation of PD-1-based combination of systemic therapy.
- Beware of immune-related adverse events on PD-1-based combinations; see patients often.
- Predictive biomarkers of response are yet to be identified.

Management of Side Effects Over the Course of Treatment

Management of patients receiving systemic treatment for metastatic RCC is complex and often entails multidisciplinary collaboration, emphasized Colleen H. Tetzlaff, MHS, PA-C, Fox Chase Cancer Center.

To illustrate this, she discussed a case report of a 58-year-old man who underwent bilateral partial nephrectomies, both of which were stage I clear cell RCC.

Ten years later, the patient developed multiple bilateral lung nodules, and lung biopsy was consistent with clear cell RCC. He was classified as favorable risk, with no adverse prognostic factors.

“Risk group guides therapy,” Ms. Tetzlaff said. “There is a clear difference in outcome among the 3 risk groups.”

Preferred regimens for this patient with favorable risk are axitinib/pembrolizumab, pazopanib, and sunitinib (Figure 1). The patient elected to receive full-dose pazopanib. The dose was reduced from 800 mg/day to 600 mg/day due to fatigue. After 10 months, he developed progressive disease.

Preferred subsequent therapy is cabozantinib, nivolumab monotherapy, or ipilimumab/nivolumab. The patient was treated with cabozantinib 60 mg/day. The most common side effects with this drug are nausea, vomiting, diarrhea, decreased appetite, fatigue, hypertension, and hand-foot syndrome. With grades 1 and tolerable grade 2 adverse events, supportive care is started and the current dose is continued. For intolerable grade II or III or IV adverse events, the recommendation is to hold cabozantinib until the side effects resolve and reduce the dose by 20 mg.

After 2 months, the patient developed mouth sores, altered taste, diarrhea, and hypertension, consistent with intolerable grade 2 adverse events. Cabozantinib was withheld and then the patient was given a lower dose of 40 mg/day.

Six months later, he had nausea, vomiting, and gastrointestinal distress. He was admitted to the hospital for severe hypomagnesemia and hypocalcemia and given appropriate electrolyte repletions as recommended by endocrinology. The drug was re-started at 40 mg/day and with daily coral calcium and magnesium supplements, the patient reported feeling much better by 1 week later. His laboratory result returned to baseline, and imaging showed stable disease.

One month later, after 7 months on cabozantinib, he developed painful blisters on his hands, feet, and legs (hand-foot syndrome). Cabozantinib was withheld and supportive care was instituted with emollients, moisturizers, and gel inserts. “With severe hand-foot syndrome, consider referral to a podiatrist or dermatologist, and narcotics for pain relief may be necessary,” Ms. Tetzlaff said.

Once symptoms resolved, cabozantinib was restarted at 20 mg/day, but it was discontinued 1 month later when the patient developed a lesion on his tongue biopsied by the Head and Neck Surgery team and consistent with metastatic RCC. At this point, he had metastases to the bone, lung, pancreas, peritoneum, and tongue.

Third-line therapy with nivolumab/ipilimumab was initiated. Common side effects with nivolumab/ipilimumab are fatigue, pruritus, rash, diarrhea, and decreased appetite. Serious adverse events include

adrenal insufficiency, hepatitis, colitis, pneumonitis, altered thyroid function, and nephritis.

Three weeks after the first treatment with nivolumab/ipilimumab, the patient developed dark urine and pruritus. A metabolic panel revealed liver function test (LFT) abnormalities consistent with immune-related hepatitis. He was admitted to the hospital and treated with intravenous steroids at 1 mg/kg. After improving, he was transitioned to oral prednisone taper. After 4 weeks, his LFTs were normalized and the steroid taper was continued. The tongue lesion resolved.

He had recurrent hepatitis while on the steroid taper, and no improvement was seen with increased steroid dose 1 week later. Gastroenterology was consulted and he was treated with mycophenolate mofetil, continued on oral prednisone, and underwent liver biopsy consistent with immune-mediated hepatitis. His LFTs normalized and remained normal after prednisone was withdrawn and the dose of mycophenolate mofetil was decreased.

Three months into the steroid taper, visceral disease was stable, but the patient had progressive disease in the bone, for which he received palliative radiation therapy. Six months after discontinuing the ipilimumab/nivolumab, his tongue lesion returned and he had evidence of progressive disease in the viscera.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Kidney Cancer give the following choices for relapsing RCC stage IV: axitinib (category 1), lenvatinib + everolimus (category 1), pazopanib, sunitinib, and axitinib/avelumab (category 1).⁶ After discussions with the patient and his wife, he chose axitinib, and it was started at a lower dose of 3 mg twice a day, rather than 5 mg twice a day give prior toxicity/side effects experienced on previous tyrosine kinase inhibitors.

Seven months into treatment, the patient had a seizure at home, and both EEG and CT results were negative. Neurology was consulted quickly, and he was diagnosed with posterior reversible encephalopathy syndrome (PRES), a risk with all tyrosine kinase inhibitors. PRES symptoms include headache, confusion, visual disturbance, and seizure, and it can evolve rapidly over hours to days.

Fortunately, PRES is usually fully reversible in days to weeks, Ms. Tetzlaff explained. Discontinue the cytotoxic agent and start medications for the symptoms. “Prompt recognition of PRES is necessary because complications can include ischemia and intracranial hemorrhage,” she said.

Axitinib was discontinued and no further tyrosine kinase inhibitor was started, because this is a class effect. After the patient recovered, he took a treatment break.

“This patient received 3 years of systemic treatment, and all his adverse events were managed with supportive care and treatment reduction, requiring a

multidisciplinary team effort,” Ms. Tetzlaff emphasized. “He has had control of his cancer for more than 3 years, thanks to multidisciplinary management.”

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advisor for Manzanita Pharmaceuticals. Dr. Michaelson has disclosed that he is a scientific advisor for Eisai Inc, Exelixis Inc, and Pfizer Inc. Ms. Tetzlaff has disclosed that she has no relevant relationships.

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