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Evidence-Based Strategies for Improving Outcomes in Advanced RCC



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With a plethora of systemic combination therapies available for treating advanced renal cell carcinoma (RCC), clinicians must critically assess clinical presentation and individual preferences to align patients with the best regimen. The standard has moved past sunitinib (Sutent), with many therapies extending survival and sometimes improving patient quality of life.

At an *Around the Practice* presentation hosted by CancerNetwork®, **Robert J. Motzer, MD**, Kidney Cancer Section head, Genitourinary Oncology Service, and Jack and Dorothy Byrne Chair in Clinical Oncology at Memorial Sloan Kettering Cancer Center in New York, New York, led a discussion with thought leaders **David H. Aggen, MD, PhD**, assistant attending physician for the Genitourinary Oncology Service at Memorial Sloan Kettering Cancer Center; **Robert S. Alter, MD**, cochief, Division of Genitourinary Oncology and Head and Neck Oncology at John Theurer Cancer Center of Hackensack Meridian Health in New Jersey; **Mehmet A. Bilen, MD**, associate professor in the Department of Hematology and Medical Oncology at Emory University School of Medicine and director of the Genitourinary Medical Oncology Program at the Winship Cancer Institute of Emory University in Atlanta, Georgia; and **Brian I. Rini, MD**, chief of clinical trials, Ingram Professor of Cancer Research, and professor of medicine (hematology/

oncology) at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee, about current challenges in the treatment of 2 patients with metastatic RCC.

Frontline Favorable-Risk RCC

CASE 1

- A patient, age 67 years, underwent left laparoscopic radical nephrectomy; pathology showed clear cell RCC, Fuhrman grade 3.
- He was on observation for 5 years without any evidence of metastatic disease.
- In 2021, follow-up scan showed multiple new lung and pancreas metastases.
- A biopsy confirmed RCC.
- Due to multifocal disease, surgical resection is not feasible.
- The patient has International Metastatic RCC Database Consortium (IMDC) favorable-risk disease.

TREATMENT

- The patient started treatment with intravenous pembrolizumab (Keytruda) at 200 mg every 3 weeks and lenvatinib (Lenvima) 20 mg by mouth daily.
- After 2 cycles, patient developed hand-foot syndrome and the lenvatinib dose was reduced; urea cream was prescribed with improvement and better tolerance.
- After 4 cycles of treatment, liver enzymes were elevated (grade 2) and both agents were held.
- Liver function test (LFT) was rechecked 3 days later and was increasing, suggesting immune-mediated hepatitis.
- High-dose steroids were started, which resulted in LFT normalization and steroids tapered weekly.

FOLLOW-UP

- Repeat scans showed complete response (CR) in lung and pancreas metastases.
- After discussing with the patient, it was decided to get imaging every 3 months and remain in observation.
- He is doing very well, with LFTs normal.
- His treatment has remained on hold for the past 6 months, and there is no evidence of disease on repeat scans.

MOTZER: Can you briefly review the TKI [tyrosine kinase inhibitor]/IO [immunotherapy] programs that are considered standard for a patient like this?

RINI: When I saw [this patient's] scans, one of my initial thoughts was maybe this is somebody we could observe. Pancreatic metastases tend to be more indolent. In terms of the IO/TKIs, patients with pancreatic metastases tend to be more responsive to angiogenesis, so I think the choice of an IO/TKI makes biologic sense here. There are 4 such regimens approved: lenvatinib and pembrolizumab, which this patient got; axitinib [Inlyta] and pembrolizumab; cabozantinib [Cabometyx] and nivolumab [Opdivo]; and then axitinib and avelumab [Bavencio]. The first 3 I mentioned have a survival benefit. They were developed in parallel with similar trial [designs], but not identical. They all provide benefit to patients; they all provide a fairly equivalent survival benefit over sunitinib [Sutent]. They also provide response rates in the 55% to 70% range, and CR rates in the 10% to 15% range. It does look like lenvatinib and pembrolizumab has higher absolute PFS [progression-free survival], response rate, and CR rate. Whether it's a truly better regimen or just differences in trials, we don't know. To me, it really comes down to a dealer's choice and comfort level with the TKI and comfort with dosing

and holding lenvatinib at 20 mg. It can be a more difficult drug, as this patient experienced, but I say that there's not 1 best choice here. It's about finding a regimen you're comfortable with and then administering it in practice and becoming an expert in that regimen.

MOTZER: Do you have a go-to regimen that you prefer?

AGGEN: It gets a bit nuanced in selecting these different therapeutics. One way I think about choosing a TKI/IO regimen is related to the half-life of the medication. Axitinib has a half-life that's in the range of about 4 to 6 hours, lenvatinib has a half-life that's about a day, and cabozantinib has a half-life that's about 55 hours. If I have a patient who has labile hypertension for whom I anticipate needing a dose hold, having a medication with a shorter half-life with more flexibility in dosing is preferred. I also think that for patients who are likely to have difficulty tolerating the highest dose of the TKI, having flexibility with the dosing is beneficial. Particularly with pembrolizumab and either axitinib or lenvatinib, you have that. With lenvatinib, we generally start at 20 mg but you can titrate all the way down to 4 mg. Similarly, with axitinib, a starting dose is usually 5 mg and there's flexibility to go down to 2 mg twice a day or up to 10 mg. With cabozantinib, the half-life is substantially longer, and for patients who are frailer I lean away for that reason.

There are also particular subgroups I think about. Based on data with cabozantinib as monotherapy, we know there's strong activity with cabozantinib and bone metastases. For patients with predominant bone metastases, I tend to favor nivolumab and cabozantinib. Although the phase 3 trials weren't powered to look at those subgroups, it does seem that there's a benefit to nivolumab and cabozantinib in patients with bone metastases. For patients with liver metastases, I tend to favor pembrolizumab and axitinib or pembrolizumab and lenvatinib in part because of the half-life issue. If patients

develop changes in LFTs, it's often difficult to tease out whether this is an IO toxicity or a TKI toxicity, so having the ability to hold that TKI is very important. I don't think about these therapies differently in terms of risk groups, and I would feel comfortable offering any of these regimens to [individuals] with favorable-risk, intermediate-risk, or poor-risk disease. I think with any of these regimens, the median time to response is on the order of 6 to 8 weeks. If you have a patient who's symptomatic, all of these are appropriate options.

MOTZER: Is there a biomarker that you use to select treatment options for RCC?

ALTER: The CheckMate 025 clinical trial [NCT01668784] did represent to us that patients with PD-L1–positive or PD-L1–negative disease still respond to [IO].¹ It has proven to us that the disease can be PD-L1 negative and still [respond to IO], so that is going to be a good biomarker. You can use blood pressure as a marker for axitinib; it seems to be isolated to that, yet we still do utilize that in our clinics. We're utilizing next-generation sequencing often and we do get information like the tumor mutation burden, which is still controversial regarding a prognostic marker for RCC. MSI/dMMR [microsatellite instability and mismatch repair deficiency] are also controversial, and I don't think we're using them very well. Right now, we don't have a good biomarker to gauge our success in how to predict response in our patients with RCC.

MOTZER: What helped you choose lenvatinib/pembrolizumab over some of the others for this patient?

BILEN: [Because] there are no prospective head-to-head comparisons nor biomarkers [for treatment], we make our selection based on clinical features. In this case, a patient has pancreatic metastases in addition to lung metastases, and we have data suggesting that pancreatic

metastasis is more [responsive to VEGF inhibitors]. This patient had IMDC favorable risk, and for this reason an IO/TKI combination will be ideal. The reason we chose pembrolizumab and [lenvatinib] is really based on patient preference. This patient is traveling a long distance and pembrolizumab can be given every 6 weeks instead of nivolumab, which is every 4 weeks. This will be easier for the patient in terms of fewer infusion center visits. In addition, this patient preferred daily medication, and you always have a hard time remembering to take medication twice a day or 3 times a day.

MOTZER: When you're discussing treatment with patients, what do you feel are the standout adverse events [AEs] that you need to talk about, and how do you follow up?

RINI: I generally talk about categories of TKI toxicities: fatigue, diarrhea, hand-foot syndrome, and hypertension. Then separately, I'll talk about the inflammatory IO toxicities, which are some of the same, such as diarrhea, although by a different mechanism. I tend to give them an overview of that, and I tend to stress that everybody's different and we're starting a lot of [individuals] at the same dose, which isn't [always] going to be the right dose. [I ask that they] give us several weeks, if not a few months, to get it right and that they need to tell us about [AEs]. We don't have cameras in their house, we're not sure what's going on, and [individuals] can get sick in a hurry, as you all know. I tend to talk in generalities about those [AEs]. I'm lucky enough to have a pharmacist who then comes in the room after me to give handouts and goes into more granular detail about [taking medication] with or without food and things like that. Then we see patients every 3 weeks when they have their infusions; at least early in these regimens, either myself or my nurse practitioner will see them. It's those first several weeks that

are critical. If patients can get off to a good start and get on the right dose of TKI, they do well. If they get off to a bad start, it just doesn't go well. They tend to want to quit the TKI altogether or end up in the hospital, and so those first several weeks are critical.

MOTZER: This patient had a dose reduction for toxicity. One of the questions that comes up when you are doing a dose reduction is about the effect on the outcome. How do you manage that question from a patient?

BILEN: I remind them that quality of life is very important and keeping them on the treatment as long as possible is also very important. If I have a patient who has a good performance status and no significant frailty, I also start lenvatinib at 20 mg, and based on the type and severity of the toxicity, we can hold or we can reduce. We are all familiar with VEGF TKI toxicity; they are very predictable. If the patient is tolerating an agent, I am comfortable that they are benefiting even if we need to do a dose reduction. But if I have a patient for whom I worry about the tolerance, starting at a lower dose and increasing it is also a valid choice.

MOTZER: What is your approach to patients who are progressing on lenvatinib and pembrolizumab in relatively short order after an initial response?

RINI: Whether their response is long or short, I'm not sure it'd be different. I tend to use cabozantinib second. I think it's the most active drug that such a patient would not have seen yet. As you're aware, we don't yet have level 1 evidence for using immunotherapy in sequence, although there are trials ongoing, so I don't do that off protocol. I tend to give a single-agent TKI; that is the default standard. If I gave cabozantinib and nivolumab up front, then of course I'd pick a different TKI, but I tend to use the pembrolizumab-based doublets that we've talked about.

Treating With IO/IO Combination in the First Line

CASE 2

- A man, age 52 years, presented in January 2021 with flank pain and hematuria.
- Medical history: hypertension, type 2 diabetes managed with metformin, obesity, asthma
- No known family history of malignancy
- CT of the abdomen/pelvis showed a 9.5 × 8.6 × 7.0-cm right renal mass with extension to the inferior vena cava.
- He underwent right radical nephrectomy in that month.
- Pathology consistent with clear cell RCC
- Surveillance imaging in August 2021 showed new mediastinal and hilar lymphadenopathy up to 5.2 cm.
- No evidence of liver or osseous metastases
- Endobronchial biopsy of a hilar lymph node showed PAX8-positive, CK7-positive, CA9-positive cells consistent with metastatic clear cell RCC.
- The patient's IMDC risk category was intermediate risk; time from diagnosis to treatment is less than 1 year.

TREATMENT

- The patient was started on combination therapy with nivolumab at 3 mg/kg and ipilimumab (Yervoy) at 1 mg/kg every 3 weeks and received 3 doses therapy.
- He developed blurry vision and eye pain with eye strain.

CASE CONTINUED

- He was evaluated by ophthalmology and diagnosed with posterior uveitis; he was started on prednisone at 1 mg/kg and steroid eye drops.

FOLLOW-UP

- Restaging CT of the chest/abdomen/pelvis after 3 cycles of therapy was consistent with partial response to treatment, with 50% reduction in target lesions.
- A subcarinal lymph node previously measuring 5.1 × 2.5 cm is now 2.3 × 1.0 cm.
- A lower right paratracheal node measures 1.1 × 1.5 cm and was previously 4.1 × 3.0 cm.
- The patient was tapered off prednisone over 8 weeks with resolution of uveitis. Patient remains on surveillance and is currently off systemic treatment.

MOZER: What were the factors that made you choose ipilimumab plus nivolumab (ipi/nivo) for this particular patient, and are there other patients with intermediate-risk or poor-risk disease that you would preferentially treat with a TKI/IO combination? What kind of factors go into that decision for you?

AGGEN: This patient is relatively young. If I were to put him on an IO/TKI combination, I'm likely committing that patient to be on a pill for months to years. In the pembrolizumab-lenvatinib study, the median time on treatment was about 17.0 months.² To commit somebody who's 52 to a TKI has some other practical risks and other chronic toxicities. For this particular patient, having a treatment-free interval was important to him. He had young children and the promise of being in that 40% of patients who are in that tail on the curve in the CheckMate 214 trial

[NCT02231749] was worth the risk of additional autoimmune toxicities.³ I will usually steer away from IO/IO therapy to an IO/TKI if the patient's really symptomatic with bulky disease and I need a response quick. In his case, he wasn't at all symptomatic from the higher lymphadenopathy, and in that case he was an ideal candidate for a combination ipi/nivo.

MOTZER: What about patients with autoimmune disorders or a history of rheumatoid arthritis?

AGGEN: It depends on the toxicity. There are certain toxicities like arthritis that are managed with topicals that you can risk challenging [the disease] with PD-1 therapy. Certainly, we're worried about an increased risk of autoimmune toxicities when we add in CTLA-4 blockade. For patients who have underlying autoimmune toxicities, that would definitely make me steer more toward an anti-PD-1/TKI combination in close consultation with other specialists who are managing those autoimmune conditions. For patients with organ transplants, my general feeling is you should steer away from any PD-1 or PD-1/CTLA-4 [inhibitor] therapy.

MOTZER: For patients who progress on ipi/nivo, what's your go-to regimen in the second-line setting?

BILEN: My default second-line agent is cabozantinib unless I have a clinical trial. There are a number of clinical trials enrolling in that patient population for different IO/TKI and TKI/HIF2- combinations. Hopefully, our options are going to get more [abundant] in the near future. If there is no clinical trial, I prefer cabozantinib either as a single agent, or if I have oligoprogression, sometimes I add it on top of nivolumab based on the first-line data. ■

➤ For references visit
cancernetwork.com/May_RCC_5.22