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RCC Treatment Strategies in a Poor-Risk Patient

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Dr. Raman:
Hi. I’d like to welcome our participants to this CME activity. My name is Jay Raman. I’m Professor of Urology at the Penn State College of Medicine in Hershey.

Dr. Akin:
Hi. My name is Dr. Oguz Akin. I’m a radiologist at Memorial Sloan Kettering Cancer Center.

Dr. Motzer:
My name’s Robert Motzer, and I’m a medical oncologist and attending at Memorial Sloan Kettering Cancer Center.

Dr. Plimack:
I’m Elizabeth Plimack. I’m a Professor of Hematology/Oncology in the division of GU Medical Oncology at the Fox Chase Cancer Center in Philadelphia.

Dr. Raman:
This CME activity is supported by educational grants from Merck and Excelixis, and I’d like to just take you through briefly this virtual activity. We are going to start with a presentation and discussion of a clear cell renal cell carcinoma patient case, and really highlight for you some treatment strategies, the evidence underlying these treatment selection options, certainly clinical considerations regarding patient comorbidities, adverse event profiles, side effects, and certainly the role and the importance of the patient in a shared decision-making model, as we manage these challenging cases. I’d like to turn this over to Dr. Motzer to start by taking us through this case.

Dr. Motzer:
Thanks very much. So this is a 46-year-old male, that had a history of hypercholesterolemia and Type 2 diabetes. He presented with lower right chest pain, and an x-ray was performed that showed a right anterior chest wall lesion. The initial CT scans showed a five-centimeter lytic lesion with a fracture involving the right anterior fourth rib, and small, bilateral pulmonary nodules. He had a CT-guided biopsy of a lesion that was consistent with metastatic clear cell renal cell carcinoma. He was deemed poor risk by the IMDC risk score, and subsequently had CT scans which revealed additional findings. Dr. Akin will present these findings.

Dr. Akin:
Thank you for the case presentation. Here we see contrast enhanced CT scans of representative lesions. On the first image, the dominant lesion is in the right fourth rib. As you can see, there is an irregular fracture line. In addition to that, if you notice carefully, along the pleural surface there is soft tissue thickening, representing that this is a pathological fracture caused by a metastatic lesion. In addition, circled with the blue line, there is a right axillary lymphadenopathy that’s very hypervascular, again consistent with a metastatic

lesion. In the second image, we see, circled with orange, a right kidney mass, again very vascular, consistent with clear cell renal cell carcinoma.

The patient's additional images showed other findings. For example, in the first image we see a hypervascular lesion in the liver, and in the second image, we see another hypervascular lesion in the pancreatic head. These lesions are also very suspicious for clear cell RCC metastases. Dr. Raman?

Dr. Raman:
So, I think as Dr. Akin highlighted, we have a patient who has a relatively smaller right renal mass, but clear biopsy-proven evidence of metastasis, and really multi-focal metastasis, both visceral as well as involving the thoracic cavity. I think when we look at these cases historically, some of the dogma was approaching up front with surgery, to theoretically debulk the tumor and thereafter treating with systemic agents. And I think over time, that has been perhaps debunked, perhaps in these specific cases, and I would cite you the CARMENA trial as evidence whereby surgery up front perhaps is not the ideal direction for such a patient. So, to briefly go over the CARMENA trial, this was a phase 3 trial in patients with metastatic clear cell renal cell carcinoma, with intermediate or poor risk, and so our patient would theoretically fall into the cohort of analysis here. Patients in this trial were randomized. They were randomized out of the nephrectomy with sunitinib or sunitinib alone, and the primary endpoint was overall survival with secondary endpoints including progression-free survival, objective response on imaging, as well as clinical benefit.

The take-home message for CARMENA was that sunitinib was non-inferior to a nephrectomy with sunitinib in the overall survival. And more importantly, when you looked at these two groups, the sunitinib cohort had a longer median overall survival, both in the overall group as well as the different subgroups of intermediate and high risk, a longer median progression-free survival, and more patients with clinical benefit. So if we take those findings back to this case, and we look at the NCCN guidelines for the management of stage 4 renal cell carcinoma, clearly we have, as shown on the top portion of this diagram, a patient with a potentially surgically resectable tumor. They have had sampling showing that this is clear cell histology from the rib lesion, and although cytoreductive nephrectomy would be technically possible, I believe that systemic therapy from some of these trials clearly is the preferred option in those patients who have poor risk features. So, I'd like to turn this over to Dr. Motzer, as well as Dr. Plimack, to take us a little bit more through the therapeutic options.

Dr. Motzer:
So this is a patient that is poor risk by our risk model, and has fairly widespread disease with a relatively small renal primary. The treatment for RCC historically would have been to do a cytoreductive nephrectomy on this patient, and treat with a tyrosine kinase inhibitor, such as sunitinib, or pazopanib, or even temsirolimus. But with the advent of immunotherapy, that paradigm has changed. The CARMENA trial spoke to the fact that patients need to be carefully selected for cytoreductive nephrectomy, and so this patient would not be a good candidate for a cytoreductive nephrectomy in view of a widespread, metastatic disease and a poor risk status. There has been a number of large, randomized, phase 3 trials that have established a new paradigm for treatment for intermediate, poor risk, and favorable risk clear cell RCC, and these have been reflected in the NCCN recommendations.

Dr. Plimack:
Well, I'll jump in and just agree with everything that's been said here. One way to think about situations like this, when patients present de novo with a renal mass, their primary place and metastases, is that your goal is long-term survival and disease-free goal. And surgery, based on the CARMENA trial, doesn't sort of move you forward towards that goal in this particular patient. I'm much more worried about the distant metastases – even though everything's small, all the lesions in this patient fortunately are small – than the renal mass. I think if we were to reframe the case and make it really large symptomatic renal mass, I imagine we would all be having a different discussion. But for this patient, I agree systemic therapy up front makes sense, and I would echo Dr. Motzer's sentiment that we move beyond single agent VEGF TKI, to really, once again, guidelines that outline combination strategies. The purporent intermediate risks – there are four with Category 1 evidence, three are VEGF TKI immunotherapy combinations, and the other being ipilimumab and nivolumab, a pure immunotherapy combination.

And so, you know, we have sort of a wealth of Level 1 evidence but that probably makes it confusing for the user of these guidelines who has more to pick from, and maybe Dr. Motzer and I can sort of outline how we think about these four options and what we're choosing for patients currently. So I'll turn it back to Dr. Motzer, and then I can comment.

Dr. Motzer:
So, I look at it, kind of as an IO-IO or a TKI-IO combination. The IO-IO combination is nivolumab plus ipilimumab, which was the first of the IO combinations to reach its primary endpoint of overall survival in the intermediate and poor risk patients, and it's the regimen that we have the longest data on, and so with that data, we really have seen long term benefit for a subset of our patients, with durable responses, maintaining progression-free survival, and maintaining overall survival with long term follow-up, now the minimum follow-up

of 42 months. So that was really the first combination that came into play, and had established itself as a standard of care. The TKI-IO combinations are all comprised of very active tyrosine kinase inhibitors – cabozantinib given with nivolumab, axitinib given with pembrolizumab, or more recently lenvatinib plus pembrolizumab. These are all very active combinations. They have high response rates, pretty much regardless of tumor characteristics, and they result in, pretty sure, a response in all patients. So I – from my own standpoint, most patients with intermediate or poor risk disease, I would favor ipi/nivo, because of the long-term benefit and the quality of life that I've seen in patients with long-time treatment. But there is certainly a role for TKI-IO combinations in patients who you really need a response quickly because they're going to run into trouble clinically, or in the favorable risk group which we can discuss later on. And I think the data for these is evolving in terms of the long-term benefit, and maybe over time that they establish the same sort of durable responses. Dr. Plimack has been key in presenting the pembrolizumab long-term benefit and that study, and I'd like to hear what she has to say about these treatment options as well.

Dr. Plimack:
Sure. So, I guess it's a little bit of a counterpoint, which is a good discussion. So, in looking at all the data from the phase 3 trials just mentioned, all of which, of course, have the background for level 1 evidence, from what I see, the long-term landmark overall survival benchmarks are hit with all the trials, the worst being 71% 2-year OS in the ipi and nivo. We're seeing 79% in len-pembro. We're not seeing really any dip in the curve with the VEGF-IO combinations. So, I guess a couple things. I'm optimistic that the VEGF-IO combinations will yield the same durable long-term benefit. I would say there is no evidence to date that they don't, and I would lean on some of the earlier trials – the phase 1 axi-pembro study that we participated in, which has really excellent long-term survival. Now with some flawed follow-up in terms of study design, but over time most patients in our clinic still alive and well, many off therapy. So, yes, we all have these patients on ipi-nivo coming to our clinics, reminding us of the success of those regimens.

I think once our clinics get populated with the VEGF-IO successes, maybe that anecdotal memory will change, so that we favor those as well. But one of the reasons I really like len-pembro as my current go-to in this situation is that we don't let patients progress on this, right? So the rate of primary progression with len-pembro is really low, like five or six percent, compared to about 17% with ipi and nivo. So, when we're treating the whole population of patients, we're looking for those early benefits as well. Same with response rate. We get a response rate of 39% with ipi and nivo, and that's 71% with len-pembro. So I would argue, yes, some patients need a response because it's of an impending problem, but even this patient, that we just discussed, with multiple small metastases – I'd love to see the rev mets shrink, and I would hate to see progression in these areas that could cause symptoms for this patient. So, I have really, sort of, sunsetted ipi and nivo, even in this intermediate/poor risk population, in favor of the VEGF-IO combinations.

I'll leave it at that. We can talk about safety, Bob?

Dr. Motzer:
So these regimens have different, distinct safety profiles. The IO-IO and the IO-TKI – both have their own kind of class of side effects that we see. With ipi-nivo, the side effects that we see are really restricted to immune-related side effects, and they are – the most common ones that we see are a skin rash, hepatitis or colitis in a small population of patients, and they are generally treated with steroids when the adverse event is moderately severe. The adverse events with ipi-nivo seem to come earlier on. In my experience, more when the ipi is given with the nivo, and I think that ipi is a strong contributor to the immune-related adverse events. When patients are treated with the nivolumab so-called "maintenance," then I've found the treatment to be very well-tolerated. I'll let Betsy talk a little bit about the TKI-IO combinations and the profile in these regimens.

Dr. Plimack:
Sure. So, what's interesting about the way we measure adverse events in clinical trials, is that it's incidence-based. So we don't have any tools that really measure chronicity of adverse events, which is really an issue when we're talking about VEGF-TKIs and even immunotherapy, which can lead to sort of chronic arthrozoes, or chronic issues related to the immune-mediated adverse events. So, the issue we run into, though, the most with patients on VEGF-IO combinations is how to decide which of the drugs is responsible, so that we can safely continue the other one, even if we have to stop one of the combinations. And generally, the recommendation for that is we stop both agents, especially in the – if you are using axitinib as the TKI. That has a very short half-life, so just holding if the issue resolves in 24-48 hours, we can pretty safely attribute it to the axitinib. Immunotherapy complications don't resolve by holding the drug, and they require close monitoring, typically steroids, either oral or IV, and sometimes additional immune-modulating agents.

So, I think when we look at incidences of toxicity, sure we can look at those numbers and compare, they look pretty similar, but in my experience, damping down the instance of a new immediate toxicity that requires steroids – that rate was about 30% in ipi and nivo, it's about half that in the VEGF-IO combinations, generally speaking. I find the chronic VEGF toxicities much easier to manage. We have experience with them. We can just modulate built-in treatment breaks, alternate the VEGF that we're using, and so I just find it a little easier to manage with the VEGF-IO combinations. Bob, I don't know if that's your experience as well.

Dr. Motzer:
Yeah, it's an area where it's a little controversial. It's not – I agree, to a certain extent, although with drugs like axitinib on long-term therapy, or cabozantinib but particularly axitinib, patients seem to exhibit diarrhea and result in frequent treatment breaks. So I think it's a different toxicity profile, with TKI-IO. It's a little more chronic. The toxicity seems to be a little bit at the – later on in treatment, that although there's some acute toxicities, where with the ipi-nivo, it's more kind of up front, with these more unusual toxicities that may be a little bit more of a challenge to manage. Different toxicity profiles, but fortunately the efficacy for either approach – and I agree, the len-pembro data was really outstanding in terms of the response rate and progression-free survival. I think that in either case, regardless of what direction one takes, the toxicity is manageable and the efficacy really speaks well for either approach with these patients. Really dramatic improvements in outcome with IO combination – either IO-IO or IO-TKI.

Dr. Plimack:
I agree, and I think, aren't we lucky to have these options, and be having these conversations, with so many active agents. I think we can think about how we talk to patients about these choices, since we do have choices, and how we use shared decision-making, what patient characteristics we sort of bring to bear when we're making some of these decisions. Again, I sort of made a bulk statement that I lean towards len-pembro in general, off studies for patients in the front line, but there are certain nuances, and obviously every patient brings a different perspective of their own, and their own sort of medical issues. So, Bob, how do you talk it through this with patients, and what issues are most important for you in these selection situations?

Dr. Motzer:
Yeah, so for the most part, for the – and we'll speak to the favorable risk patients later, but for the intermediate and poor risk patient, if it – I discuss both options, and I – len-pembro, and ipi-nivo, because I don't think that – kind of one-size-fits-all, and I think different patients may have preference for one versus another. And again, if it looks like a patient is going to run into trouble, then I definitely favor the len-pembro because of the high response rate. But for other intermediate or poor risk patients, I do think over a long term, with the evidence that we have and with the quality of life I've seen from most patients on IO therapy, that I favor ipi-nivo.

I do think that part of the choice depends on the physician's comfort in giving a regimen, so to your point, I think that many oncologists are comfortable giving TKIs because they've given TKIs for years and in terms of managing side effects, TKIs may be more familiar with management. For others who have given a lot of ipi-nivo, like myself, I'm very comfortable with managing these immune-related side effects. So I think, you know, part of it is the patient preference, and also physicians' comfort in terms of delivering therapy and managing toxicity, as well as the disease characteristics.

Dr. Plimack:
Yeah, I would agree with that. I think, in general, you know, intermediate and poor risk patients generally do have comorbidities. In the trials, they generally, you know, each patient came with their own issues and yet across the board, we see benefit with the trials we've just discussed. So there's no – other than, sort of, red flags for immunotherapy, that would give us pause in using it at all. There aren't real patient considerations that would make me decide between the different agents. But one nuance I would add is that axitinib is a really easy-to-dose titrate TKI. It also has the shortest half-life, so if we run into trouble, just stop and it wears off. Lenvatinib, which in combination with pembrolizumab, has an arguably somewhat better efficacy, especially in the up-front endpoint, is a little bit harder to dose titrate, given the strength it comes in, and also has a longer half-life, so wears off slower. So I think for someone who I'm really ginger about starting, VEGF therapy, I might favor an axitinib combination.

Dr. Motzer:
So, I'd like to pass this over to Dr. Raman and Dr. Akin for their insights into the case, and – Dr. Raman?

Dr. Raman:
Yeah, I think as a urologist, you know, where does this patient maybe circle back? So, you have a young patient – clearly we've talked about the importance of systemic therapy, and both of you have highlighted very well the different regimens and the decision-making. And so, in many cases, where do we see these patients come back? Well, they're young, they've hopefully had a favorable response in their metastatic sites of disease, and the question that arises is what to do with the primary lesion. And, you know, I would largely say that I think the role of surgery still remains fairly limited here. I think, as Dr. Plimack highlighted, sure, if you have a patient with a bulky renal mass, perhaps one who is symptomatic, perhaps one who has hematuria, then I think the indications for surgery are for symptom control. I think for any reason, if you have a patient who's coming off of systemic therapy, or somebody who's demonstrated growth of the primary lesion while on systemic therapy, despite having metastatic sites that have stabilized, another consideration for a treatment option at a local setting, whether that's surgery, or image-guided ablation.

And the final point would be in these cases, we do like to think about the potential, if at all possible, for a partial versus radical nephrectomy, just to render them with the most amount of renal reserve. For subsequent treatments, that may occur down the line, or

other comorbid conditions that may arise. But I would say the role of surgery, both up front, but even in the interval setting, is really for fairly select cases and unique scenarios. Dr. Akin?

Dr. Akin:
Thank you. So, imaging will be, again, important to follow-up these patients during the course of treatment. As we see in this case, there's some lesions, they are clearly metastatic, which could be chosen as target lesions for monitoring the treatment. However, again, as we see in this case, there are some smaller lesions which could be also – which should be also closely followed, because progression can occur on both subtle lesions as well, and the choice of imaging really depends on the patient. CT is usually sufficient for most patients, but smaller lesions, such as a liver lesion for characterization. Depending on the case, other imaging modalities, such as MRIs could add to clinical assessment, if needed. Other than that, I think the imaging follow-up is mostly very straightforward for these patients.

Dr. Motzer:
Alright. In terms of – so, you know, final kind of thoughts on the case. It sounds like the consensus would be to defer a cytoreductive nephrectomy, and start therapy with an IO combination, either ipi-nivo or lenvatinib-pembrolizumab, as Dr. Plimack spoke to. And I think that it's going to be an individual choice, either one is an excellent option, with a possibility of a deferred cytoreductive nephrectomy at some point, if a patient has an excellent response.

Dr. Plimack:
And I would just add also the possibility of discontinuation of treatment, if the patient has an excellent response. I think, in the ipi-nivo trial, nivo maintenance continues indefinitely until there is a reason to stop it. But in the VEGF-IO trials, IO, at least with the pembro studies, ends at two years. And many of us feel comfortable pausing the VEGF-TKI at that time as well. And we're populating our clinics with success stories who have long-term, treatment-free survival, from all these groups of patients. So, look forward to a time when we can treat patients for a finite period of time and then have them maintain durable disease control off therapy.

Dr. Raman:
Great, well, I'd really like to thank all of our panel members today, and certainly to thank our attendees and our learners for joining us, and I'd like to remind our attendees to please complete the post-test, as well as the evaluation, to receive CME credit for this activity. Thank you.

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