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RCC Treatment Strategies in a Favorable-Risk Patient

Announcer:
Welcome to CME on ReachMD. This activity, entitled “RCC Treatment Strategies in a Favorable Risk Patient” is accredited by Penn State College of Medicine, and sponsored by The Academy for Continued Healthcare Learning. This activity is supported by independent medical education grants from Exelixix, Inc. and Merck and Company, Inc. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Raman:
Hi, I’d like to welcome our participants and our attendees 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 an attending radiologist at Memorial Sloan Kettering Cancer Center in New York.

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

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

Dr. Raman:
This CME activity is supported by educational grants from Merck and Exelixix, and to just give you a virtual tour board activity overview of what we’re going to be talking about, this is going to be a presentation and a discussion of a patient with clear cell renal cell carcinoma. We’ll talk about treatment strategies, some of the evidence that’s underlying the selection or the recommendations for potential treatment options, certainly clinical considerations including patient comorbidities and adverse event profiles of different treatments, and most importantly, perhaps, the role of the patient in a shared decision making process, as these treatment selections are made. I’d like to turn it over to Dr. Plimack to take us through this case.

Dr. Plimack:
Sure. So, this case is a 62-year-old woman who initially presented in 2016 with a left clear cell renal cell carcinoma. At the time, she also had a metastasis to the ipsilateral left adrenal gland.

Dr. Raman:
So this is a situation that we see a lot in the kidney cancer world after urologic surgery. Certainly, these patients who pathologically have nonmetastatic disease, but have high-risk features – T3, T4, perhaps N1 disease – and ultimately, the question is, what is the role, especially as our armamentarium has grown, for the use of adjuvant therapies for high-risk nonmetastatic kidney cancer? And I’d like to turn it over to Dr. Motzer and Dr. Plimack, because we certainly refer our patients to medical oncology for consideration and discussion of trials and options. Perhaps their thoughts for this patient at this juncture.

Dr. Motzer:

Well, I can – I'll speak first to tyrosine kinase inhibitors, and then perhaps Dr. Plimack can cover the IO programs, but the tyrosine kinase inhibitors were looked at, maybe 10-12 years ago, as an adjuvant therapy in large Phase 3 trials, compared to placebo. There was one trial – the S-TRAC trial that showed a modest benefit for sunitinib in prolonging disease-free survival, but the others, particularly the ASSURE trial, which was a larger trial done in cooperative groups in the United States, as well as studies with sorafenib, axitinib and pazopanib, failed to show a benefit. So although technically sunitinib has received regulatory approval in the United States, really there's a body of evidence showing that TKIs really don't benefit patients. And with the toxicity, I think that we were looking for new avenues, and generally I don't recommend sunitinib as an adjuvant therapy for our patients. I think that the real excitement and enthusiasm now is with IO therapies, and maybe Dr. Plimack can comment on that.

Dr. Plimack:
Sure. So, we've been excited about adjuvant immunotherapy strategies in renal cell for a long time. We've shown that in melanoma, this can be a successful strategy, and we just recently saw at ASCO, data on pembrolizumab after a section of high-risk renal cell carcinoma, that showed a disease-free survival benefit. Currently, the data on overall survival is immature, meaning not enough people have died, which is a good thing, on the study to say whether we're helping people live longer or not. Very exciting. I think a lot of us think that immunotherapy has much more potential to be of benefit in the adjuvant setting, but personally, until we have overall survival data with this strategy, I would hold off. Rationale being that we want to cure people if we're going to expose a broad group of patients, including those who are destined to never recur, to the toxicities we discussed in a prior case, of immunotherapy. And second of all, the combination strategies for metastatic disease are so effective, it's possible that that may shrink the difference between the curves when we look at OS. So I'll wait eagerly to see those data.

Let's continue with the case. So this patient, of course, underwent surgery, as we discussed. At the time, in 2016, there was no FDA-approved adjuvant therapies, so this patient would have gone on to just regular surveillance. And in 2019, she was found to have hepatic nodules, with biopsy consistent with clear cell renal cell carcinoma. After discussion with her treating physician, she elected to go on surveillance, meaning no treatment but serial imaging to follow the low-volume metastasis, and this was based on shared decision making and patient preference. In 2021, so now two years later, there was continued growth, new metastases, increased total tumor burden, but when we calculated her IMDC score, she is favorable risk. So I'll pass to Dr. Akin to take us through the images.

Dr. Akin:
Here we see the represented images from the most recent CT scan. The first image shows multiple bilateral pulmonary and pleural based metastases, in the lower lung sections. In addition, there is moderate sized right fluid effusion compressing the right lung. We see a lymph node in the left aortic region. Although this lymph node is about a centimeter in size, if you notice, it's enhancing very avidly. In a patient with clear cell RCC, this is, again, very suspicious for metastasis. Now I'd like to pass it over to Dr. Raman for surgical options in a patient like this.

Dr. Raman:
Sure, so I think you are limited. And I would say, when you look at recurrent kidney cancer, where does surgery or perhaps SBRT really factor in? I think it's really when you have a solitary site of metastasis, where perhaps metastasectomy allows you to treat that lesion, and perhaps delay or obviate the need of systemic therapy. The reality is, when you have a patient such as this, who has multiple metastases in the lungs, evidence of lymphadenopathy in the periaortic distribution, this again highlights systemic disease, and systemic disease really needs systemic treatment. And so I pass it back to Dr. Plimack and Dr. Motzer, really to take us more through the algorithm of how they approach this with systemic therapy considerations.

Dr. Plimack:
So, this is a different scenario, this favorable risk patient than an intermediate and poor risk patient. And in this particular patient case, she was on observation for a period of time before enough lesions grew to really introduce a recommendation for systemic therapy. Now, the data are clear that combination immunotherapy – VEGF or IO combinations – will yield benefit in this scenario in terms of progression-free survival and response rate, over single agent VEGF-TKI. But, interestingly, consistently across the VEGF-IO trials, there's no yet overall survival benefit in the favorable risk group, with these therapies over a single agent VEGF therapy. So, in a patient who, again, doesn't need that benefit of response rate, maybe less is more, maybe has concerns about immunotherapy or can't come to the center for infusions. In that group of patients, one could, with shared decision making, discuss starting with VEGF-TKI first, again, for convenience and limiting side effects.

Given that, you're not sacrificing anything in terms of overall survival. But it's a discussion with each patient. Dr. Motzer?

Dr. Motzer:
Yeah, so I agree. The surveillance approach for favorable risk was really established before there were effective drugs, based on the really variable natural history for kidney cancer, where some patients would have very aggressive course, and other patients would

have slowly progressive disease, or even spontaneous regression. So I think that many of our patients who are asymptomatic, with small volume disease, are followed by surveillance until it's clear that the patient's progressing or requires therapy. The criteria for that really have not been objectified. It's really more subjective, and again, it's a decision between the treating oncologist and the patient. For the favorable risk patients, my preference has been to go with a TKI-IO for the majority of patients, albeit there are, as Dr. Plimack mentioned, there's options of a TKI monotherapy or even ipi/nivo in this population of patients, but I favor the TKI-IO, based on the high response rate, and the overall activity of the combination in the trial, recognizing that the trials weren't powered for a survival benefit in this relatively small subset of patients. But also, this gives me the opportunity to DC either the TKI, and continue the IO therapy if the patient's not tolerating that, or vice versa – if there's a poor tolerance to the IO therapy, then I DC it and continue the TKI. I also favor this approach because the progression-free or the disease-free survival is longer with these combinations. And I think patients are traumatized by progression while on one or the other therapy. So I think – that's been my approach for most patients, but recognizing that frail patients or patients who do not want IO, immune therapy given IV, could be treated with a TKI alone.

Dr. Plimack:
So, I would agree with that. I think the only thing I would add is that if we don't want patients to progress, we have really no business using ipi/nivo in favorable risk patients. The response rate is much better with even single-agent sunitinib, and we know we can improve even further upon that with the combinations of VEGF-IO. The progression-free survival curves with very long follow-up still show superiority of sunitinib over ipi/nivo in favorable risk, and again, there's no overall survival benefit with any of these, but ipi/nivo falls into that category also. So I agree, I think if you're really looking for the most benefit, short term and long term, the combinations make sense. It's really an individual patient where single agent VEGF-TKI would be used. I think the data comparing the different trials – it's important to note that in the intent-to-treat population, all of the trials showed superiority over the single agent VEGF-TKI. The subset analysis for favorable risk, while clearly a subset analysis that's post hoc in most cases, does help us with individual patient decision making, and I think what Dr. Motzer described, and hopefully we covered with this patient, is that especially in favorable risk, these are some of the longest shared decision making conversations, because of all the various aspects, and also because usually our hand is not sort of forced with a threat of symptomatic progression. These are patients who have lived with disease for a long time, with a good quality of life – in this patient's case, observation – and so decision making happens sort of slower, over a period of time, with more options. So I'll go back – turn it to Dr. Raman for insight.

Dr. Raman:
Yeah, I mean, I think the two sort of take homes that I would have from this are, certainly in the upfront setting, post-surgery, I think it's really important for these patients with high-risk, nonmetastatic disease to see a medical oncologist and to discuss the merits of therapy, particularly with some of the data coming out with IO therapy. And then, I'm sure Dr. Akin would agree, but I think the other really important component is realizing that a lot of patients with high-risk, nonmetastatic disease will unfortunately recur, and that's been proven out just with data, with risk calculators, and certainly evidence-based imaging and staying on imaging algorithms is critical to identify recurrences at an early time point, and clearly before they become symptomatic, where I think the disease outcomes are inferior. Dr. Akin, your thoughts?

Dr. Akin:
I definitely agree with what you said. One point I'd like to add. If you notice, this patient stayed on imaging surveillance for a very long time, and as radiologists, we are often asked to compare the recent imaging with the most recent prior imaging study. But in patients like that, with multiple lesions that are slowly growing, it's very critical to look at the baseline scan as a comparison, and go back and compare every single lesion, because progression can occur in different lesions at different rates.

Dr. Plimack:
Absolutely.

Dr. Raman:
Any final thoughts, Dr. Motzer or Dr. Plimack?

Dr. Plimack:
I guess I agree with that imaging recommendation. I think we can get tricked when scan after scan says stable, but when you look back over years, there's really progression. And this makes the conversation sort of, again, in the assessment of each favorable risk patient observation, more complex. But it's a good problem to have. Again, the longer we keep patients on observation, sometimes the better treatments we have for them when they do need to start, or access to clinical trials, so there's that padded benefit of observation as well.

Dr. Motzer:
Yeah, I would agree that imaging is key for following these patients over time. It's also very important to have a radiologist who is familiar with the disease to follow the images and give insight into the rates of progression.

Dr. Raman:
Well, I really want to thank, again, all of our panel members for their thoughts and their insight, certainly to our attendees and our learners for joining us, and I would remind all to please complete the post-test as well as the evaluation, to receive your CME credit for this activity. Thank you.

Announcer:
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