Transcript Details

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Advancing Care in Non-Clear Cell RCC: Optimizing ICI and TKIs

Announcer:
Welcome to CME on ReachMD. This activity titled 'Advancing Care in Non-Clear Cell RCC: Optimizing ICI and TKIs' is jointly provided by the France Foundation and the Kidney Cancer Association. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Announcer:
Welcome to the activity, 'Advancing Care in Non-Clear Cell RCC: Optimizing ICI and TKIs,' brought to you by the France Foundation and the Kidney Cancer Association. This activity's presenting faculty are Dr. Pedro C. Barata, Miggo Family Chair in Cancer Research at Case Western Reserve University in Cleveland, Ohio, and Dr Sumanta K. Pal, Professor and Vice Chair of Academic Affairs at City of Hope Comprehensive Cancer Center in Duarte, California.

This activity's learning objectives are recall the importance of accurate diagnosis and classification of nccRCC, compare and contrast clinical trial data on current and emerging uses of ICIS, TKIs, and combination ICI/TKI therapy, describe the rationale for combination therapies and treatment sequencing strategies in nccRCC, identify approaches for monitoring AEs associated with ICI and TKIs in nccRCC.

Next, Dr. Barata will provide an overview of nccRCC.

Dr. Barata:
When we think of kidney cancer, we really think of a global disease. We have over 434,000 new cases diagnosed as of recent data that puts kidney cancer the 14 most common disease diagnosed, and is really a universal problem. You can see the, you know, the incidence, you know, in different geographic locations around the world. On the right, you see the incidence is going up. Number reasons for that. One of them is, you know, access to care that allows us to diagnose more cases of kidney cancer.

Now, when we try to organize kidney cancer, meaning tumors that started in the kidney, we call them renal cell carcinoma. I really like this schema because it reminds us of the histopathologic characteristics from different tumors. We know that 3/4 of the times will have clear cell, and then the rest of those tumors will be non-clear cell. We understand that they derive from different portions of the nephron, as you can see here represented. Today, we'll be focusing on the varying histologies that are non-clear cell RCC.

So among those non-clear cell subtypes, papillary RCC is the most common one. So in general, we're thinking, you know, papillary followed by chromophobe, translocation, and then all the other rarer forms of RCC. So that's really, you know, when we are looking at the epidemiology data, that's really what we should expect to see.

Now, we have a number of different guidelines put together to help us with the optimal management of this disease. In here you're looking at European guidelines, ESMO guidelines. I like them with these guidelines, because it does remind us of a couple of things, easy or important things. One is the importance of having tissue to make the diagnosis of renal cell carcinoma and the subtype. It's really important to call out the underlying subtype, as well as calling out the presence of sarcomatoid and/or rhabdoid dedifferentiation. It allows us to give you prognostic information as well as predictive information, because it does have therapeutic implications. So really

go for tissue, try to call out the subtype, and try to get an information about sarcomatoid and rhabdoid features.

Now, we know that these tumors have or present with key differential molecular pathways, so those are different for each subtype. I think, in this graph or this schema here, rather, you can see the difference gene expression signatures based on the different RCC subtypes. So for example, more angiogenic signature there for clear cell and then, you know, we have increased for cell cycle or fatty acid synthesis for certain types of non-clear cell subtypes. So really, a combination of different cancers within this larger group umbrella of non-clear cell subtypes. And of course, that makes the management and treatment considerations a little more challenging.

Here's a table to kind of make our life a little bit easier, right? You can see that one important aspect of this new classification is the addition of molecularly-defined RCC subtypes. And this is the ESMO guidelines that I showed you before, does reflect this new WHO 2022 classification, which actually, by the way, replaced the previous 2016 classification. And there's important changes, right? One of them is the historical type 1, type 2 papillary RCC is no longer advised. So we no longer call out type 1, type 2 papillary RCC; type 1 now we refer as classic RCC, the type 2 are now grouped into broader categories that might include clear cell or papillary tumors, or, you know, a molecularly-defined renal cell carcinoma.

You also have a list of these molecularly-defined RCC subgroups such as FH-deficient RCC or SMARCB1-deficient medullary carcinoma, as well as the former, you know, the TFE3 and TFEB, they're now distinct subtypes of altered RCC; they used to be called translocation RCC as a whole, right? So we do have changes to the WHO classification that one needs to be aware of.

It's also important to recognize that some of RCC tumors are a reflection or a manifestation of a broader hereditary disease or known familial genetic mutation, which is also can be associated with other cancers. So, for example, tuberous sclerosis, more commonly than not, you get angiomyolipomas, but we know there's an increased risk for renal cell carcinoma, both clear cell and non-clear cell. And this, of course, in the context of mutations in the gene TSC1 or 2. We also have examples of FH-deficient RCC; used to be known as hereditary low myomatosis in RCC. Of course, you can have different manifestations of the disease, including renal cell carcinoma. And we have a few others in the table for your reference as well.

With that in mind, we should think of who are the patients we could consider genetic testing, specifically germline testing, in other words, testing the genes you were born with and were passed on from father and mother, you know, and patient got them and throughout their body. So that germline testing, it's important, and you have a number of recommendations, you know, that can be put together about who are the patients that would deserve germline testing. And here's a list of them, right. There are things that we know. You know, if patient diagnosed with a renal tumor and had a first-degree relative with RCC or renal tumor and patient has a second-degree relative with undocumented germline mutation, or you cannot as the first-degree relative, or you have RCC subtype that's suggestive of specific genetic-related RCC, such as FH-deficient or even multifocal chromophobic RCC. For example, you know, bilateral tumors, you can think of that younger patients, you can think of that, you know. Those are just a few examples of the paper from Dr. Bratslavsky and colleagues in Cancer a few years ago, kind of give you a recommendation about who to do germline testing.

Announcer:
Key clinical trial data in nccRCC.

Dr. Barata:
And for that, we'll start with a patient presentation. So think of a previously healthy male in late 60s presenting to his primary care with persistent unexplained flank pain and hematuria. He underwent initial workup, including CT scan of the abdomen and pelvis, showing an 8-cm mass in the right kidney with invasion of the renal vein, so automatically makes us think of a T3 disease. There's no evidence of distal metastasis on imaging. He actually has no significant past medical history, no known family issue of cancer. And you know, he's a former smoker with occasional alcoholic use.

So giving the presentation, you know, and imaging, you've got to be thinking of renal cell carcinoma, it's going to score high in your differential. But there's other chances of this being something else, like oncocytoma or angiomyolipoma as well. And so for that you, you know, patient underwent a biopsy, percutaneous core biopsy of the renal mass, which reveals non-clear cell RCC, specifically papillary subtype. And further molecular testing is pending at their time. Patient is staged as a T3, N0, M0; T3 because there's invasion of the large renal vein. It's discussed at tumor board, and at this time it was considered for a number of options. They were debating the role and the merits of surgical resection versus active surveillance versus ablation.

And patient ultimately underwent robotic-assisted partial nephrectomy for that kidney mass and pathology report comes out and calls out a grade 3 papillary RCC with sarcomatoid features and vascular invasion of the renal vein, negative margins, and patient has a MET amplification. So tumor board got back together to discuss adjuvant treatment options.

And so the question is, for this patient with high risk of recurrence, what treatment would you consider?

If I were to walk you through some of the conversations that took place at tumor board, of course, folks would be thinking about whether or not a TKI could be considered. Right? We have data in a metastatic setting with PAPMET showing improved outcomes with cabozantinib versus sunitinib for patients with metastatic papillary RCC. Again, remind you that we don't have data in the adjuvant setting with a TKI. We also debated the data around savolitinib, which is a MET inhibitor, also showing promising activity again in the metastatic setting, no data in the adjuvant setting. Finally, you could be savvy and bring up the data with a combination of immunotherapy with TKIs, whether it's lev/pem or cabo/nivo. We'll be talking about that later today. But again, you would be extrapolating data to the adjuvant setting from the metastatic setting, what that data was developed. You could also review other pieces of data out there to justify your decision. You will be discussing the limited data, the absence of data in the adjuvant setting, the potential benefits and risks of adjuvant treatment, monotherapy versus combo, and also patient's interest and, you know, what you should be doing.

So, with that said, in the context of no evidence of data to prevent cancer from coming back in papillary RCC, the decision was to offer active surveillance to this patient with regular scans to check on his status. And he ended up getting scans every 6 months to make sure or to rule out recurrent disease.

Now, when we think about clinical trial data for non-clear cell RCC, and of course, that will include a lot of different RCC subtypes, you could think about different treatments out there that we might be using in the metastatic space. You could be thinking about monotherapy checkpoint inhibition with pembrolizumab. You could think about combos with the TKI and IO, cabo/nivo, lev/pem. You could be thinking about ipi/nivo combo. You have data to support that. Or even triple therapy with cabo/ipi/nivo. Those are considerations about when we think about varying histologies.

Going into the specifics. So here on these two pieces of data, you can see the support of immunotherapy. On the left, pembrolizumab alone is data from Dr. McDermott, progressive-free survival in the 4.2 months, not really long. Although there were interesting responses, you know, 1/4 of patients responded and a median overall survival that exceeded 2-year mark. For the combination of cabo/nivo, you really have a median progression-free survival over a year, 13 months, although the median overall survival looked similarly numerically, a little bit over 2 years, 28 months median. When you also look at responses, these responses very close to 50%, very close to another IO/TKI, responses in the 48% range, if you will.

And it's kind of similar to what we've seen in the other combination IO/TKI with lev/pem, where you can see median progression-free survival of 18 months for this combo, and thinking about while the median overall survival is not reported at that time, most patients were alive at 1-year mark, over 80% of patients, to be specific, or were alive at 1-year mark. Promising results with both cabo/nivo and lev/pem in the setting.

Now, you also can think of other combinations. Here on this slide you can see on the left, data with triple therapy, cabo/ipi/nivo. These study is an investigator-initiated study. On this trial, patients had a median time to progression of almost 10 months, with an objective response rate of about 21%. A different combination also the TKI lenvatinib, but this time with an mTOR inhibitor, everolimus, lev/ev, which is approved also for clear cell RCC. And here, we've seen time to progression, progression-free survival of 9.2 months with objective responses of 26% and 15.6 months of median overall survival.

And finally, thinking of checkpoint inhibition combos with ipi/nivo, you know, this is data that have been presented in the SUNNIFORECAST just less than a year ago, we've seen median progression-free survival of a little bit shy from 6 months, 5.5 months to be precise. And also, when we're looking at the median overall survival, you're looking at 42 months, and 86%-87% patients alive at 1-year mark. So also promising results. You know, it's interesting to see on this data, in particular, you can see the curve separating at 1-year mark, which justifies the positive endpoint for this study, although down the line, the curves for survival kind of get together. So you know, no statistical significance was found between ipi/nivo and the standard of care in this particular trial.

Announcer:
Key clinical trial data in common nccRCC subtypes.

Dr. Barata:
Let me walk you through some specifics for some of the subtypes that we see more often. So let's start with papillary RCC, which accounts for up to 15% of the cases. We know that it originates in proximal or distal caveolated tubules, and again, type 1, type 2 papillary RCC is no longer recommended. Now, the morphology is heterogeneous, and you can find molecular markers that can help you identify the different types of papillary RCC. MET plays a role in papillary RCC, and although you have many tumors who are MET independent, who have another molecular markers playing a role in this setting.

So data for papillary RCC, you can look at different combinations, or TKIs monotherapy, or combinations with mTOR, or mTOR by itself. So different things. Here you can see data for cabozantinib, you know, for savolitinib, for everolimus, sunitinib, and then combo such as

lev/ev or erlotinib/bevacizumab, which is data out of the NCI.

So we cannot say there's one regimen favor compared to the others, because we don't have a phase 3 trial comparing the different regimens, as you can see from this table. Although most patients will be considered for TKI monotherapy, some might be considered for a combination, whether it's erlotinib/bevacizumab or lev/ev, if you're not thinking of the combination of an IO/TKI, who has shown promising activity, responses close to 50% as you can see on this slide. And that reminds us that there might still be a role for immunotherapy for papillary RCC.

Now, looking into the specifics for this data, the best randomized trial might be the PAPMET SWOG effort, SWOG1500 compared 150 patients to cabozantinib or sunitinib. Initially it was actually a four-arm study, but the arm savolitinib and crizotinib were discontinued due to fertility, so it became a head-to-head study of cabozantinib versus sunitinib. And as I mentioned before, high response rate, higher PFS. It was a positive trial for cabozantinib, although we don't appreciate a statistically significant difference between cabo and sunitinib in regards to overall survival.

Now, on the right, we have data by Dr. Choueiri showing us proof-of-concept data on savolitinib which is a MET inhibitor. You definitely see the differential activity of savolitinib for MET-driven disease compared to MET independent, 6.2 months PFS compared to 1.4 months for patients with MET-independent disease, 18% responses versus zero. So clearly stresses out the role of MET, you know, for a MET inhibitor.

You can build upon that combination of savolitinib with immunotherapy. Promising data from Dr. Suarez and the group, PFS of 12 months, median overall survival 2 years. This actually leveraged a larger phase 3 trial ongoing. On the right, as I mentioned before, this is data from the NCI group, Dr. Srinivasan showing promising data for bevacizumab/erlotinib combo. And that data for the sporadic papillary RCC 8.8 months. And the data is even more impressive for patients with so called hereditary leiomyomatosis, where you actually see a very prolonged median overall survival. So definitely combination to keep in mind. Moving on to chromophobe RCC, so you can account for 5 to 7% of all RCC cases. They're mainly sporadic, but they can be associated with certain hereditary conditions such as Birt-Hogg-Dube syndrome or Cowden syndrome. It actually develops additionally in the nephron. I think I showed you that earlier today, compared to other RCC subtypes, and actually has a small risk of metastasis. You know, so a lot of the patients actually get cured with local therapy.

And here's a table put together some of the regimens we just mentioned on the prior question. You have comparison specifically for mTOR, you have comparison of everolimus with sunitinib, combinations of mTOR, everolimus/lev, or lev/ev, excuse me, or ev/beva. And then you have other combinations with TKIs and IO, such as cabo/nivo or lev/pem, or even epi/nivo or cabo/ipi/nivo. So you can see here that definitely mTORs, we see a signal with mTOR inhibitors in these type of tumors. We also see some activity with IO/TKI such as lev/pem. We do see a little bit of activity with immunotherapy by itself, although more modest than we tend to see in clear cell.

So in general, I would say that combination can be considered. We do consider those quite a bit. I would also say that mTOR, part of the regimen you're choosing for your patient is completely appropriate to be considered for chromophobe RCC.

Moving on to translocation-associated RCC. Accounts for up to 4% of all cases, and actually more than 1/3 of all pediatric RCC and 15% of the younger patients are likely to have this type of tumor. It originates in epithelial cells of the tubule, of the proximal tubule, and is characterized by a chromosomal translocation, typically the chromosome Xp11.2. This actually tends to behave quite aggressively, with a widespread metastatic disease and poor prognosis.

One more time, we put together the data to support different regimens for patients with translocation RCC. You can see here that, in opposition to what we've seen before in mTORs, we don't see as much of a signal compared to chromophobe. You do see some activity with TKIs. We see promising activity of combinations that includes an TKI with a checkpoint inhibitor. So it is true that in many cases, patients are being considered for an IO/TKI, like in this particular setting, based on the data that's available. And we will leave it here for your reference.

So if I go, you know, through the details of these data here, you can see that on the left with atezo/bev one more time here, you know. And then we have data on the right, more retrospective data in regards to activity of immunotherapy TKIs versus IO/IO. In this retrospective dataset, real-world dataset, it appears that the IO/TKI provided higher response rate, even though the median overall survival wasn't that different. This particular experience on the right, it's mainly US experience here. So you have data beyond clinical trial as well to support IO/TKI in this patient population.

Moving on to collecting duct, it can account for up to 1 to 2% of the cases. It develops from distal collecting duct principal cells, and characterizes by a tubulopapillary architecture, stromal aplasia, and high nuclear grade. It also retains SMARCB1 gene, which differentiates this subtype from the SMARCB1-deficient medullary carcinoma. But what it has in common with medullary carcinoma is

actually the poor prognosis and, in general, treatment resistance. So actually, this collecting duct is one of the cancers where I usually break the rule. I usually tell kidney cancer patients that we don't use chemo, and that's actually true, except in collecting duct, you can consider chemotherapy with a platinum-based regimen. There is some data with TKI and IO. The data is not particularly meaningful for the IO. We do see some activity with cabozantinib. That's an Italian trial data or experience. And as I said, chemotherapy doublets can be considered with some activity, although usually not long lasting.

Here's a breakdown of the data for the two regimens that I consider gem/cis or carbo/gem with PFS of around 7 months, response is 26%. Cabo monotherapy response is seen in 35%, although median progression around 4 months. The median overall survival for the regimens is way less than a year. Gem/cis, or gem/carbo trial, was 10.5 months and was actually shorter than that on the, you know, single-arm cabo trial, with 7 months median survival.

So let me present you the same case. I'll summarize it for you. Let's get back to our case. So again, man in the late 60s presented with that T3 kidney mass, no metastatic disease. At the time, you offer partial nephrectomy, margins were negative. It was a grade 3 papillary RCC with sarcomatoid features which the tumor showed MET amplification. Patient underwent surveillance. Unfortunately, a year later, the restaging scans showed a new 2-cm nodule. Biopsed confirm, you know, metastatic papillary RCC.

So that's actually a good segue for us to revisit treatment sequencing strategies for patients with non-clear cell subtypes. Right? As you can see here, frontline regimen is usually preferring a clinical trial, if available. I would say, not to forget the role of local therapy in patients with oligometastatic disease or oligo-recurrent disease. So for example, if this patient were to have one spot of disease only, you could actually think of radiosurgery perhaps, or resection perhaps, you know, if feasible in that situation, right? And of course, when you look at disease progression, it depends on you consider upfront. We can have a conversation around sequencing therapy for patients progressed on frontline. We don't have a huge ton of data, so we go by what regimens have shown activity, and let's use a regimen that we have not used previously.

What does that mean? So when I pull up the slide for systemic therapy for non-clear cell, you can see here preferred regimen trial, and then you have cabozantinib, followed by/or cabo or IO/TKI, like cabo/nivo or lev/pem. So you know, and I do a lot of cabo/cabo/nivo based on the data that I've shown you before. However, there are other recommended regimes that can be recommended for selected patients. For example, erlotinib/bevacizumab for selected patients, if you're thinking about hereditary leiomyomatosis, or even mTOR or immune checkpoint inhibition, that's there. Other options can be useful in certain cases, like an mTOR, everolimus, or the combination of bev/ev or even ipi/nivo. If you think of trial data and NCCN guidelines, you would accept as reasonable options, the combination of cabo/nivo, everolimus, radiation to the lung nodule, especially if it's oligo-recurrent disease, or even nivolumab monotherapy. So actually, tumor board got together to discuss this case, and patient is not eligible for a clinical trial. There's no trial available at the center at that time, so the patient end up getting cabo/nivo combination. And so he did. He was started on cabo/nivo.

In these patients, it’s important to monitor for response and also new toxicities with dose adjustments as needed. I'm sure by now, you guys are getting very familiar with managing adverse events from the combination, and you’ve got to do that, and don't forget to get restaging scans on a regular basis. So we could justify the combination based on the data from the metastatic setting, but keep in mind that we are extrapolating from the phase 3 trial, 9ER cabo/nivo in the clear cell, and also we're using phase 2 proof-of-concept data for non-clear cell, 48% response, which is the data I just showed you before.

So the case reminds us the importance of considering clinical trials for patients and also underscoring the importance of tailoring treatment decisions, and it's important to take disease characteristics into equation, high treatment history, overall health status. Of course, just a reminder that it's very helpful for these rare forms of cancer, bring it to the group and have a conversation as a group about what to do. Not all cases are easy to handle, and so you want to make sure you have this data in mind and you can debate this as a group.

So with that, we got to the end of this first part of two parts. I'm going to pass the baton to Dr. Pal, who will take us over the next sections of this talk around non-clear cell RCC. Thank you so much.

Dr. Pal:
So let's discuss some of the rationale for combination therapy. We have monotherapy regimens for a non-clear cell renal cell carcinoma that yield response rates in the ballpark of th3ree to 27%, we have doublet therapies, which in single-arm studies yield a response rate of 20 to 48%, and triplet therapies, which ironically, seem to have a lower response rate. The progression-free survival range is quite wide. Here you can see that with monotherapy studies, it ranges up to 8.3 perhaps 11 months with doublets, and 9.7 months with triplets. And we don't really necessarily see overall survival as a reasonably assessed endpoint across many of these single-arm studies. But having said that, you can see a wide range as demonstrated there.

I wanted to highlight the data from the triplet regimen, since I think that will garner a lot of interest in this setting. Brad McGregor has led

a triplet study looking at the combination of cabozantinib, nivolumab, and ipilimumab. Ironically, although you'd think that this would have the highest of the response rates, the response rate here was only 21% with a median progression-free survival of 9.5 months, and overall survival wasn't yet reached. Now, certainly this data warrants further maturity. We'll see how that pans out.

When we look at retrospective data here, this is an important assessment across the Memorial Sloan Kettering cohort. What you can see is that, for instance, in chromophobe renal cell carcinoma, it looks as though TKI with IO may have an edge. But you know, again, things that are important to consider here are the bias in terms of our timeline of therapies. These therapies were introduced more recently when we had better supportive care measures. All of these things might potentially help boost the observed progression-free survival. And I'll point out that there's relatively limited numbers of patients who are receiving the combo.

The ORACLE study is an interesting trial published by Deepak Kilari and presented at the ESMO 2024 meeting. And this looked at a variety of different non-clear cell subtypes. You can see a range of response rates. So for instance, what's kind of ironic here is that if you look at dual checkpoint inhibition in chromophobe disease, you see a response rate of 50%, I don't know how reliable that is. There's a relatively small number of patients there. For papillary renal cell carcinoma, you see a response rate of 15%. And for unclassified, you see a response rate of 31%.

In contrast with TKI in combination with checkpoint inhibitor, you see a response rate of 28% in papillary, 28% in chromophobe, and 40% in unclassified subtypes. Finally, in patients with a combination of VEGF and mTOR inhibitors, it looks like there's not a lot of responses in papillary patients, but if you go to the chromophobe subtype, you see a very healthy response rate of 76% that I found to be very intriguing.

So if you look at the guidelines, as per the NCCN, you can see that, and this is a really important point, clinical trials are always preferred in this setting. It also suggests that the patients consider the possibility of metastasectomy if they have oligometastatic disease, and radiation. I always try to look to that for my patients. When it comes to preferred systemic therapy regimens, you can see that cabozantinib-based regimens are preferred in the frontline, just as this patient had received that patient that we considered received cabozantinib/nivolumab.

Lenvatinib with pembrolizumab is also a possibility in that frontline setting. When you get to the next line of therapy, you can see that lenvatinib and everolimus, sunitinib, all the choices that we saw in the previous slide, are really encompassed as potentially options that are recommended or useful in certain clinical circumstances.

Now, what about the other guidelines? These are derived from the EAU guidelines, and I find it to be a little frustrating when you look at these guidelines, even though they are there to help guide therapy. One of the things that we see is that, you know, for instance, in the context of metastatic papillary renal cell carcinoma, cabozantinib, which has randomized data associated with it, is still given a weak recommendation. Lenvatinib with pembrolizumab or cabo and nivo are also given a weak recommendation. And I guess that makes sense. I mean, that's on the basis of single-arm phase 2 clinical trials. These aren't randomized datasets in those contexts.

For the other non-clear cell subtypes, you can see, again, the data is listed as being weak. You can see that sunitinib is a recommendation that's given weekly here. Lenvatinib and pembrolizumab is weekly. It is something certainly that I think we need to consider in the context of patients with non-clear cell disease.

Now, what do the EAU guidelines tell us and the ESMO guidelines in terms of sequencing therapies? These are the ESMO guidelines here for papillary renal cell carcinoma. So when we look at this in a disease-specific context, you can see that cabozantinib is listed as a preferred therapy, but they do mention alternatives of sunitinib, alternatives of pembrolizumab, and in fact, sunitinib was actually given the same footing. So I do think that there's room for randomized trials using a sunitinib control arm here, at least for the time being. There are systemic therapies that can be used if they haven't been given previously, and that includes agents such as cabozantinib, sunitinib, everolimus, and possibly pembrolizumab.

What about the other non-clear cell subtypes? So there's also some guidance from ESMO on this. And what you see in that context is, if patients have advanced disease, if they've received therapy in the context of chromophobe renal cell carcinoma, sunitinib, pazopanib, lenvatinib-based therapies, all these are listed as options. As we piece through the data, as we've highlighted previously, I tend to be a proponent of looking at lenvatinib-based therapies here. Collecting duct and medullary are a unique beast, where we still consider cisplatin-based chemotherapy, and there seems to be some emerging evidence for cabozantinib as Dr. Barata shared. For sarcomatoid disease, you can see that at the ipilimumab and nivolumab tops the list. You probably will hear a lot of consensus from many investigators around that, but TKI/IO combinations are also very reasonable in this setting.

So we're going to consider the scenario of a previously healthy male in his late 60s. This patient presented with persistent unexplained flank pain and hematuria. The patient had workup with a CT scan of the abdomen and pelvis showing a 6-cm mass in the right kidney.

Patient had no evidence of any distant disease found on imaging. And this patient ended up going under a robotic-assisted partial nephrectomy. All the margins were negative, and we found a grade 3 papillary renal cell carcinoma with sarcomatoid features. And of course, the tumor, as we often see in papillary renal cell carcinoma, showed MET amplification. So this patient started to undergo surveillance thereafter, and about 15 months later, we saw that there were new bilateral 1- to 3-cm lung lesions. We did a biopsy and confirmed this patient had metastatic papillary RCC. We've discussed previously some of the choices that we have in this scenario. So this patient was started on therapy with cabozantinib and nivolumab. We had close monitoring of toxicities and treatment response in this case.

And what we found in this scenario is that the patient ultimately did develop grade 2 diarrhea. So when we think about grade 2 diarrhea, think about the CTCAE grading system. This is the way that we typically assign grades in this scenario, and that would, by memory, involve four to six palliative events above the patient's typical norm. So remember, diarrhea is based on the quantity of stools per day, as opposed to stool quality, which oftentimes confuses our patients. This patient also had hypertension.

So the question becomes, how do you manage these toxicities? These in my mind, and we haven't assigned a grade to the hypertension, wouldn't necessarily be dose-limiting toxicities unless the hypertension was very severe and required the onset of multiple new agents or hospitalization. In this case, we used loperamide for the patient to manage diarrhea, and we also did the dose reduction of cabozantinib. So when you're using cabozantinib in concert with nivolumab, remember, that's at a dose of 40 mg daily. You have the option of coming down to 20 mg. And if the patient still has diarrhea, you can come down even further, to 20 mg every other day. In this case, the patient used loperamide as well, which is a very good first step. Diphenoxylate is another agent that can be used in the refractory setting. This patient also had hypertension, which was management anti-hypertensive agents. We used to have lots of discussions around what the optimal anti-hypertensive was for patients, but frankly speaking, I don't know if there is one that pairs well, if you will, with therapy with a TKI. I think that you just have to basically choose based on clinical intuition. You can use beta blockers, you can use ACE inhibitors. All of these classes of anti-hypertensives are very reasonable.

I think this case really underscores the importance of proactive toxicity management. You know, many times, what I see is that a patient, when I see a second opinion, cycles through therapies really quickly at the first onset of a toxicity. But it's important to keep in mind that if we actually focus on strategies like dose reduction, using supportive care strategies to mitigate toxicity, we can really improve quality of life. We can optimize treatment outcomes. We don't necessarily need to discontinue drug in the vast majority of cases.

Announcer:
Adverse effects of treatment.

Dr. Pal:
Now, there are many common side effects that are associated with TKI use. Diarrhea is the one that really comes to the fore. I think that that's quite common with cabozantinib and lenvatinib, for that matter, as compared to other TKIs, those are some of the more nonspecific targeted therapies. Hand-foot syndrome I do see more often with cabozantinib, I suppose, as compared to others. Hypertension is something that we tend to see with the more sort of specific VEGF inhibitors, and that includes agents such as sunitinib or perhaps dovitinib. And hypophosphatemia can be seen across the broad spectrum of therapies for non-clear cell kidney cancer.

The timing, I think, is so key to consider. If you're using an immunotherapy-based regimen, it's important to bear in mind a timeframe in which you might potentially observe some of these side effects. It's different than when you're using a TKI, where the side effects can be more immediate. So if you're seeing a patient who's on a checkpoint inhibitor, some of the things like rash actually emerge fairly quickly. You might see that come up in 4 to 6 weeks, for instance, as highlighted here. Colitis, on the other hand, might emerge after the 4-week mark, and it tends to peak at around 3 months or so. I always tell patients that it's right around the time the first scan assessment when we start running into issues.

I do agree with what you see listed here, in the sense that there are certain delayed toxicities. So for instance, pneumonitis can occur very late in the ball game. I've also seen toxicities like nephritis occur very late. And also endocrinopathies. I've seen those come about very late in the course of treatment. And it's really a call for us to continue to survey patients with scans, to continue to survey their laboratories as they're going through, to make sure that they're not have any latent effects of immunotherapy. It's a very big consideration in clinical practice.

There are some treatment-related adverse events that are more common to TKIs, though. And as we've already highlighted, that includes things like hand-foot syndrome, hypophosphatemia, and fatigue. The rates of grade 3/4 toxicity here are not insignificant. As you can see with first-generation agents such as sunitinib, which I have listed on the right there, you can see that there are about 69 to 81% of patients who are going to have grade 3/4 adverse events. And there are some treatment-related deaths that can be associated with it, as you can see there. I would suggest that, on the other hand, with more modern agents and contemporary agents such as

cabozantinib, the side effect profile is better, albeit not perfect. With lenvatinib and pembrolizumab, I think it's important to bear in mind the risk of hypertension, proteinuria, and stomatitis. I'd also add on to this list, colitis, which is something that I tend to battle with lenvatinib-based treatments. I'll say that with savolitinib, liver dysfunction is something that we really need to be very mindful of. I've also seen extremity swelling in that particular concept, definitely something to bear in mind.

So what can you do if you have a patient with advanced kidney cancer? What are some of the important resources that are out there? I really am so proud of being a part of many advocacy groups for kidney cancer. The Kidney Cancer Association does tremendous work, and you can see that they have a side effect tracker. These are ways that patients can potentially track common side effects, whether it's diarrhea, hair color changes, hoarseness of voice, and recognize those and bring them up to providers at the time of their visits. And it's a really wonderful way for patients to communicate with their physicians as they come to subsequent visits.

The NCCN also has some wonderful guidelines related to management of autoimmune-related toxicities. I like these, as well as the ESMO guidelines if you're struggling at all with the management of liver dysfunction due to checkpoint inhibitors or skin-based toxicities, as I often do, I think it's really important to refer to these guidelines frequently to get some good guidance.

I think there's a lot of value in coordinating multi-disciplinary care. If you're at a hospital with limited resources in terms of gastroenterology or dermatology, I think chances are you're going to see these sorts of side effects pop up as you increase your use of checkpoint inhibitors. So it's incredibly vital that you try to build some bridges to local specialists and providers who have expertise in those areas. If you have a suspicion for these side effects emerging, whether it's diarrhea or dermatologic, I would suggest that you really get plugged into your respective specialties very early, so that we're not rushing at the last minute trend to try to engage our colleagues.

So in summary, non-clear cell kidney cancer, molecular assessment and genetic risk assessment are really vital. The World Health Organization classification of urinary and male genital tourism 2022 added some really important subcategories. Treatment recommendations vary across international guidelines and in clinical trials of multiple non-clear cell subtypes. It's really those combinations of TKIs and checkpoint inhibitors that elicited the highest response rates. That being said, those are single-arm trials, and it's really important to bear in mind that if the patient is eligible for a clinical trial, that's the best way to go. In clinical trials for papillary RCC, TKIs have elicited the highest response rates. There's some potential for therapies that are based on MET status, although that's still pending. And finally, for treatment-related adverse events, very, very important to bear these in mind during the patient experience and use resources like those provided by the Kidney Cancer Association to help mitigate and manage side effects.

I want to thank you all for your attention as we move into the posttest.

Announcer:
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