Transcript Details
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Elevating the Standards of Care: Key Considerations Guiding Treatment for Patients with Advanced Renal Cell Carcinoma

Announcer Intro:
Welcome to *Project Oncology* on ReachMD, sponsored by Exelixis. Here's your host Dr. Paul Doghramji.

Dr. Doghramji:
This is *Project Oncology* on ReachMD. I'm Dr. Paul Doghramji, and joining me to discuss some of the key factors guiding treatment decisions for patients with advanced renal cell carcinoma is Dr. Wenxin Xu, a physician at the Dana-Farber Cancer Institute and an Instructor in Medicine at Harvard Medical School. Dr. Xu, welcome to the program.

Dr. Xu:
Thanks, Dr. Doghramji. Happy to be here.

Dr. Doghramji:
Excellent. So let's begin with some background, Dr. Xu. Can you give us an overview of the treatment guidelines for advanced renal cell carcinoma according to the national comprehensive cancer network?

Dr. Xu:
Yes, absolutely. Looking at the NCCN guidelines for kidney cancer, I think a couple of things to start; one is that the NCCN guidelines, because the field is moving so fast, has been changing every rapidly every few months. And so it's possible by the time you hear this program, the guidelines may not be the same version that I'm looking at now. That being said, when you look at treatment for advanced kidney cancer, I think the first thing to remember is that not every patient needs systemic therapy right away. And so the guidelines would support for some patients pursuing active surveillance if they don't need immediate treatment. And this is supported by a prior phase 2 trial that was led br. Brian Rini where patients who had active surveillance and no symptoms from kidney cancer had a median time to treatment of about fifteen months, even longer if they had good risk factors. Similarly, some patients who have advanced or metastatic kidney cancer prior to starting systemic treatment might benefit from local treatment whether that's metastasectomy, or radiation, or nephrectomy for selected patients. But if you look at patients who do need systemic therapy for kidney cancer, the next question is to see if they have clear cell or non-clear cell kidney cancer because these are completely different pathways to go down.

Dr. Doghramji:
And bringing those guidelines into real-world clinical practice, how does our current approach to treatment take disease-related factors, such as risk of progression and comorbidities, into consideration?

Dr. Xu:
Right. So, you know, the guidelines are based off of the best clinical evidence we have, but when a patient is sitting in front of you, you really have to make a decision for that patient. And so there's several questions that I always ask myself when I see a patient. Number one, is the patient symptomatic from their disease? You know, we always treat cancer with two goals, to prolong life, but also to improve the quality of life and treatment can't improve the quality of life by definition if the patient is asymptomatic from disease. And so for some patients with low disease burden and no symptoms from disease, you really have to question how much toxicity you're willing to risk from the systemic therapy. Similarly, as I alluded to before, some patients may benefit from local therapies, which may delay or sometimes even indefinitely the need for systemic therapy. This has become very, very controversial ever since the CARMENA study was published a few years ago looking at upfront nephrectomy versus systemic therapy in patients with metastatic kidney cancer. But there probably are still some patients that benefit from either up-front or debulking nephrectomy, especially if they're having symptoms from a renal mass or if the renal mass represents the vast majority of the total burden of disease.

Other patient factors you have to take into consideration are whether there are high-risk specific metastatic locations that need to be dealt with first. For example, brain metastases can become symptomatic very, very fast and some patients may need local treatment such as radiation or surgery to brain metastases before they start systemic therapy.

Independent of all that, once we've decided we are gonna start systemic therapy, you really have to look at the overall clinical risk and risk stratifications scores like IMDC or the MSKCC risk score can help us with this. Separately, patients may have side effects from treatment, and you must consider comorbidities from other diseases the patient may have. We know that patients with existing autoimmune disease are much more likely to have immune checkpoint-related toxicity. Similarly, patients with strokes or PEs or uncontrolled hypertension might be at higher risk from the vascular comorbidities or side effects that you see from VEGF receptor TKIs.

Dr. Doghramji:
OK. So now along with disease-related factors, I'm sure patient preferences also pay a role in our individualized approach to treatment. So how can we prioritize those preferences?

Dr. Xu:
So patients nowadays have a lot of resources available to them: information on the internet, information from other patients, from patient advocacy groups. And patients more and more are coming to us with a lot of information and highly educated about their cancers. Now patient preferences come down to a few different areas. I think one question I get asked a lot by my patients is 'What is the impact this disease will have on my quality of life? Can I continue living the kind of life that I'm living?', and some patients may still be working, and some patients may need to travel for example.

Another thing to consider from the patient perspective is how much symptoms they're having from their disease and how much they need to have those symptoms palliated by treatment. And conversely, if the patients do not have a response to first line treatment, whether they will get so sick that they cannot advance to second line therapy. And so for this, you really have to look at not just a response rate, but also the disease control rate and the risk of progression of disease during the initial therapy. And, you know, looking at this, for example, when you look at the combination of VEGF receptor TKIs and immunotherapies, these are the combinations that tend to have the higher rates of up-front disease control. For example, greater than 88% of the patients with up-front disease control on cabozantinib and nivolumab, whereas with combination immunotherapies, ipilimumab and nivolumab, there's probably a slightly higher rate of patients who will have progression of disease despite first line treatment, even if some of those patients who have response may have long-lasting responses.

Dr. Doghramji:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Paul Doghramji, and I'm joined by Dr. Wenxin Xu to discuss some key treatment considerations for patients with advanced renal cell carcinoma. So Dr. Xu, now that we've talked about some of the key factors to consider when building a treatment plan, let's take a look at what happens after we initiate therapy. What do we need to think about when managing adverse events?

Dr. Xu:
So we know from clinical experience that both immunotherapies including checkpoint inhibitors and VEGF receptor TKIs, anti-angiogenic therapy can have substantial side effects. And the side effects differ between these two different classes of medications.

So among the VEGF receptor TKIs, common side effects include high blood pressure, palmar plantar erythrodysesthesia or rash on the palm and soles, diarrhea, and other vascular toxicities, which can include major bleeding for patients who are having surgical procedures. In comparison, patients who are on checkpoint immunotherapies can develop immune-related adverse events, commonly including fatigue, rash, diarrhea, but also other toxicities that can involve any organ system, including pneumonitis, hepatitis, thyroiditis, and others. And so we really have to be vigilant and understand that dose delays and dose reductions are very, very common in patients on these types of therapy. When you look back at prior phase 3 trials, the majority of patients on either VEGF receptor TKIs or checkpoint immunotherapies had one or more dose delays or dose reductions. When you just look at immune-related adverse events, many of these patients will require systemic steroids to manage their toxicity. When you look at single agent immunotherapy with PD1 or PDL1 inhibitors, about 20% of patients will receive steroids for one or more immune toxicities. When you look at combination immunotherapy with ipilimumab and nivolumab, that rate is gonna be higher. And looking back at the phase 3 CheckMate 214 clinical trial that compared ipilimumab and nivolumab to sunitinib, in the immunotherapy arm 46% of patients had grade 3 or higher adverse events. So we really have to be ready and vigilant and recognize these side effects early because they're highly treatable.

Similarly, as clinicians, the onus is on us to understand the regimens that we use most commonly, to know what the dose reductions are for the medicines that we're using, and especially for immunotherapy, to get to know our consultants, including the gastroenterologists and the dermatologist and the pulmonologists so that when we have toxicity, we know who to call.

Dr. Doghramji:
Now before we close, Dr. Xu, we've obviously talked a lot about disease-related factors and patient preferences. So to bring all this together, can you talk about the importance of taking an individualized approach to treatment and how those factors play a role?

Dr. Xu:
Right, so when I think about individualized treatment, individualized treatment can mean psycho-social and patient factors, what the patient prefers, and it also means individualized biology. What is it about this patient's overall health and their tumor biology that might lean us one way or the other? When you look at patient preferences, some patients may put a higher weight on disease control up front, while other patients may put a higher weight on quality of life, and other patients might really, really want to maximize the chance of a long-term response to first line therapy. And that is especially true for some of my younger patients, who in the absence of cancer, are looking at potentially years and years of life ahead of them. Other patients may have limited access to healthcare. I have some patients who live far away from any hospital, and you really have to take that into account when you're prescribing a therapy that could possibly cause life-threatening immune-related adverse events for example.

When you look at biology, I think we're learning more and more about individualized biology in these patients. I think biomarkers are an area of active research. There's still a lot to do. I don't think we're quite there yet for picking the precise biologic therapy for each patient. But one could imagine, probably not everyone may need to get every treatment and some patients would respond better to immunotherapies versus VEGF receptor-directed therapies. And we have some emerging data that we might be able to personalize some of these decisions based on mRNA gene expression signatures, mutation patterns, and other tumor specific data.

At the end of the day, what we know is that some patients with metastatic kidney cancer can have durable, long-term responses with not too much toxicity. And the question on us, as clinicians, is to really figure out how to increase that number and give more patients a chance at a more normalized and longer life.

Dr. Doghramji:
Well it's clear from our discussion today that there are a lot of factors to consider when treating patients with advanced renal cell carcinoma. And I wanna thank my guest, Dr. Wenxin Xu, for joining me to share how we can incorporate them into our patient treatment plans. Dr. Xu, it was great having you on the program, today.

Dr. Xu:
Thank you so much, Dr. Doghramji. It was so nice to be here.

Announcer Close:
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