INTERPROFESSIONAL COLLABORATION WHEN MANAGING PATIENTS WITH GENITOURINARY CANCERS

Q1. How can the members of the care team work together in the clinical-decision making process to improve outcomes in patients with genitourinary cancers?

Q1 Answer:

Marcus: Hi, I'm Marcus – I'm the pharmacist. As the medication experts, pharmacists can help by remaining well versed in the multiple indications, and different combinations, and dosing strategies associated with the multiple immunotherapy agents. Then this knowledge will allow them to help the clinicians in deciding what's going to be the appropriate regimens that patients can use based on their type of cancer as well as the stage of disease. Additionally, pharmacists can play a role in managing different immune-mediated adverse events (AEs) by counseling patients regarding which types of events might be appropriately treated with over-the-counter (OTC) medications, such as topical emollients or oral antihistamines for pruritus, for example.

Laura: That's great, Marcus. I'm Laura - I'm an oncology nurse, and similar to the role that you do, Marcus, as the pharmacist, in many oncology practices, education regarding cancer therapies, potential side effects, and side effect management is done by a nurse. And nurses as well are very familiar with the immunotherapy agents and spend a significant amount of time with patients and their family members while administering these drugs. Others are managing telephone triage, taking intake calls, and coordination of the patient's care and sometimes that involves multidisciplinary coordination as well. So, all of these go together to improve outcomes in the oncology setting. Often these nurses in the infusion and rooming areas are eyes and ears of the other oncology team members because of these frequent interactions. They may very well, Marcus, be the first to identify side effects that may require a discussion amongst the oncology team as to whether or not treatment interruption or the addition of supportive strategies are appropriate, thus playing a key role in clinical decision-making.

Q2. In what ways does the oncology pharmacist's role complement the roles of other team members such as the oncology nurse, the oncologist, and oncology advanced practice providers?

Q2 Answer:

Marcus: As part of the team, I fell that me as the pharmacist can help provide education to other healthcare professionals, such as Laura and other nursing staff as well as the physicians, regarding different immune-related adverse events (irAEs) and how to manage them, especially since certain toxicities we see, like hypothyroidism, are pretty unique compared to what we see with traditional cytotoxic chemotherapy, where we would expect things like neutropenia and other bloodline abnormalities. Pharmacists can also help review the patient's medication profiles to notice any significant drug-drug interactions, particularly when we start talking about different oral targeted agents later on, and recommend dose adjustments to the oncologist based on these drug interactions and a patient's changing lab values.

Laura: I agree completely, Marcus. It's very much a resource that we appreciate, having the pharmacist available to assist with decision-making. In many ways our roles overlap, but everybody brings their own expertise to the team. That's the wonderful thing about oncology – that collaboration between oncology

providers. There is a large need for education of our team, as new drugs come out, as we learn more about the dosing strategies and the dosing strategy approval changes, it's important for every member of the team to know that. I think it's also a great thing that when I learn something from my pharmacist, I can turn around and share that with an infusion nurse or clinic rooming nurse tomorrow. So, the education is really ongoing. Our oncology pharmacy staff is great at answering questions regarding the immunotherapy regimens, and things to be aware of and those nuances. And the pharmacist in our out-patient pharmacy, because we're blessed to have an out-patient pharmacy, is a great resource regarding the drug interactions like you talked about, with our oral oncolytics as well as the options for side effect management. In particular, a shout-out to the pharmacist because when I get a denial on a medication and the patient's insurance won't cover it, I'm able to call the pharmacist and say "OK, this is what's occurred, what other alternatives might we have a better chance of getting approved on?" So, it's great team opportunity.

CASE 1: GLENN: RENAL CANCER

Case: Glenn is a 68-year-old male is referred to a medical oncologist for the management of new lung metastasis 9 months following a radical nephrectomy for clear cell renal carcinoma. He has a history of hypertension which is well-controlled, and lab tests demonstrate mild anemia and mild chronic kidney disease results from his prior nephrectomy.

Q1. Is Glenn in the favorable or intermediate risk group according to the International Metastatic Renal Data Base Consortium (IMDC) criteria?

Q1 Answer:

Marcus: Looking at the IDMC criteria, Glenn would definitely fit into the intermediate risk group based on the fact that he has a hemoglobin that's below our lower limit of normal and he's developed metastatic disease 9 months following his initial diagnosis. Just as a reminder, some of the other laboratory factors we would consider here are having an elevated corrected calcium, and elevated neutrophil count or an elevated platelet count, and then other clinical factors that could feed into this are if he had a low Karnofsky performance score less than 80%.

Laura: Thanks, Marcus. Yes, you know we see approximately 50% of the patients that are diagnosed with kidney cancer fitting into that intermediate risk group. Based on historical data, these individuals have a median overall survival of 27 months, and a 2-year survival of 53%. What's important and exciting is that checkpoint inhibitor therapy, whether it's ipilimumab plus nivolumab, or avelumab plus axitinib in a combination strategy, or pembrolizumab plus axitinib where we're combining a checkpoint inhibitor and a vascular growth factor tyrosine kinase inhibitor, the oral agent, these therapies are really starting to improve the median and overall survival for this intermediate risk group.

Q2. Based on the NCCN guidelines, what immunotherapy treatment options should be considered?

Q2 Answer:

Marcus: Based on what the NCCN has so far, all three of the approved immunotherapy regimens would actually be appropriate for Glenn in this first-line setting. Pembrolizumab plus axitinib versus sunitinib demonstrated a 24-month overall survival of 74% with the pembrolizumab plus axitinib arm compared to 66% with the sunitinib arm. And then looking at objective response rates we see response rates we see about a 50% higher rate, so we see 60.2% with the pembrolizumab plus axitinib arm compared to 39.9% with the sunitinib monotherapy.[Plimack ASCO 2020] Additionally, when we look at avelumab plus axitinib we see a median 12-month survival of 86% compared to 83% with the sunitinib.[Motzer 2019] And then comparing the immunotherapy combo therapy of ipilimumab and nivolumab, we see a 12-month overall survival of 83% compared to 77% with sunitinib.[Motzer 2018] So all of them showing some benefits in the overall survival.

Laura: Yes, the data is really impressive, Marcus, and we're really making changes in survival and progression-free survival for our patients. It's nice to be able to talk about 12-month and 24-month survival data. It's important to understand that these clinical trials started at different time points and so the data is continuing to mature and the results are continuing to be updated. And we're continuing to see improvements in overall survival and long, durable response rates.

One of the key things for shared decision making and patient involvement, Marcus, is determining what is the appropriate treatment, not only in the front-line treatment setting, but we're still striving for long-term disease control with a good quality of life, and that's important as we talk as a team and decisions need to be made regarding treatment interruptions, dose reductions, and when treatment fails requiring new treatment decisions to be made. It's very much a collaborative effort; we look at the most current NCCN guidelines, and nurses and pharmacists very much participate in these discussions, helping patients and their loved ones navigate these difficult situations.

Q3. What would you want to discuss with Glenn regarding potential side effects of treatment?

Q3 Answer:

Marcus: Here is where I think it's really important to have that intercollaborative approach with Laura or another nurse to make sure that we're getting the full education to Glenn and his caregiver, whether that be a significant other or someone else, we want to talk about treatment with the combo arm of pembrolizumab plus axitinib. We want to talk about the rationale for why we are combining two agents and why it's potentially synergistic combining the mechanism of one, a checkpoint inhibitor, pembrolizumab, with the VEGF effects from axitinib and how it can lead to enhanced antitumor activity so enhancing our immune cell activity against the tumor, we can increase the antigen presenting cell effect, enhancing tumor infiltration, and decreasing the effect of suppressor cells and macrophages in the tumor microenvironment.[Allen 2017] Of course, we would work together to make sure we explain it in a way that's understandable for the patient and making sure they understand that it's really a two-pronged approach; that we're going to use them together because we get better results when we use them together. Then once they understand the rationale of why we need two drugs, we would go on to discuss the therapeutic goals of his treatment, how long he can expect to be on treatment, and any potential side effects.

Laura: I definitely agree, Marcus, and it's an ongoing educational approach, and that's where you alluded to that collaborative education. It's important to help the patient and their caregiver understand the complex information regarding how each of those treatment drugs contributes to the overall treatment plan. I use a lot of analogies, as well as written educational information, in order to facilitate that learning process because what you and I provide during clinic visits and infusion visits needs to continue once they get home. The written information reinforces that. Patients and caregivers need to be educated about potential side effects because they're only going to be in the clinic intermittently, and they're going to need to be our eyes and ears at home. And so that's critical at the initiation of therapy and at every patient/caregiver interaction. We know that immune-related adverse events can occur at any time from day 1 to long after they have stopped receiving checkpoint inhibitor therapy. Because inflammation is a hallmark of the irAEs, that communication needs to be early and ongoing in order to minimize long-term negative impacts on treatment. If we don't catch them early enough, we may not have the opportunity to intervene and get them back on therapy. Disease control is important because we're still working towards curative therapy. IrAEs such as rash, itching, fatigue, and lab abnormalities are a few of the immune-related adverse events. Then in combining the pembrolizumab plus axitinib, Glenn needs to understand the specific side effects associated with the VEGF inhibitor therapy, axitinib including hypertension, and the need for blood pressure assessment, when to call regarding onset or worsening of any existing hypertension, hand-foot syndrome, and voice changes. Some of these become more significant and impact nursing and treatment interruptions. Then there's the overlapping between the immune therapy and the VEGF therapy. I think one of the advantages in this combination regimen is the fact that axitinib is an oral drug, it's taken twice daily; and dosing can easily be interrupted to allow side effects to improve. As well as the fact that the dose of axitinib can be modified to ensure tolerability, rather than be discontinued. I would strongly encourage practitioners to work with their patients to identify a tolerable dose of axitinib, and a dosing strategy and supportive care, rather than discontinuing it should the patient have difficulty with side effects. There are going to be those patients where no matter how much effort you put in, one or the other therapy has side effects that are too severe or intolerable and the drug needs to be discontinued. In this case then one of the drugs can be continued on alone, but it's relevant that data continues to demonstrate the importance of a combination compared to monotherapy, as demonstrated in the clinical trials. Again, often times the written information is also developed in a collaborative effort between the pharmacist and the nursing staff to be able to reinforce the treatment plan once the patient and caregiver are at home, again, that continued education

CASE 2: SANDRA: UROTHELIAL CANCER

Case: Sandra, a 70-year-old female with a 40 pack-year smoking history, presents to her urologist with complaints of increased urinary frequency and mild hematuria. A CT scan of the abdomen and pelvis, CT urography, and transurethral resection of the bladder (TURBT) are performed, which confirm the diagnosis of high-grade NMIBC with urothelial carcinoma in-situ (Tis). Post-TURBT, she undergoes adjuvant therapy with intravesical BCG; however, follow-up cystoscopy shows persistent disease at 3 months. She undergoes repeat TURBT and receives a dose of intravesical gemcitabine within 24 hours. A discussion is had with her regarding the possibility of radical cystectomy, which she declined.

Q1. Based on current NCCN guidelines, which immunotherapy agent(s) would be most appropriate to consider for Sandra?

Q1 Answer:

Marcus: Since Sandra has come back now with BCG-unresponsive, non-muscle invasive bladder cancer with tumor in situ, the only recommended immune checkpoint inhibitor at this stage would be the pembrolizumab, based on the KEYNOTE-057 trial, which was the basis for NCCN addition and FDA approval. She would be treated for up to 24 months, assuming she didn't progress on therapy and there were no unacceptable toxicities. While the SWOG S1605 trial [Black 2020] did show some promising early data using atezolizumab in this setting, this study still hasn't reported long-term outcomes such as progression-free survival, overall survival, and hasn't yet been either FDA-approved or recommended by the NCCN, so we wouldn't consider it at this stage.

Laura: Yes, and as we think about the immunotherapies, we know that the evolution of these drugs has been very interesting. The early clinical trials, even the pivotal studies that have led to FDA approval, have been followed by additional approval of extended dosing intervals. Nivolumab was initially approved at a 240 mg given IV every 2 weeks, subsequently it was extended to 480 mg every 4 weeks. In a similar situation, pembrolizumab was initially approved at 200 mg with IV infusion every 3 weeks, and again was recently extended to 400 mg every 6 weeks. The good news is that these changes were not just in genitourinary cancers, but across almost all malignancies, with a few exceptions. I think it's important as we all recognize the challenges are significant with the COVID-19 pandemic these extended infusion times so that patients don't have to come to the infusion center as frequently has been a critical benefit for not only clinicians, but also patients and family members with a decrease in the number of patients needing frequent infusions and a decrease in the frequency of those visits.

Q2. She declines immunotherapy at this time, and instead is agreeable to adjuvant intravesicular therapy with weekly gemcitabine for 6 weeks. If she progresses to locally-advanced or metastatic disease, which immunotherapy agent(s) would be appropriate per NCCN guidelines as first-line treatment? Are there any factors to consider before selecting an immunotherapy for first-line treatment?

Q2 Answer:

Marcus: This is one of those cases where we need to consider, if she has locally-advanced or metastatic disease, the first thing we want to think about is whether or not she is eligible for cisplatin or any platinum therapy in general. Factors that may make her ineligible for cisplatin therapy are any significant renal function impairment at baseline, that would be creatine clearance (CrCl) usually less than 60 mL/min, or any hearing impairment, or any pre-existing neuropathies, since we know cisplatin can potentially exacerbate these. Complete ineligibility for platinum therapy, meaning she wouldn't be eligible for carboplatin either, would be if there was severe renal impairment (CrCl <30 mL/min), in which case the toxicity profile might outweigh the benefit that she can receive. If we determine she is cisplatin-ineligible, then PD-1 testing should be performed to determine if Sandra is eligible for a checkpoint inhibitor. The cut-off would be a PD-L1 greater 5% for atezolizumab or PD-L1 CPS of at least 10 if we want to use pembrolizumab. If we determine she is completely platinum ineligible, meaning she

has such significant renal function impairment that she wouldn't be eligible for either platinum agent, then we can proceed straight to checkpoint inhibitors without any baseline PD-L1 testing.

Laura: That's an important point that you bring up, Marcus, as far as the need for clinicians to understand that there are some very unique nuances in treating urothelial cancer, and that there are criteria that help determine a patient's appropriateness to receive a platinum-based therapy; not all patients are appropriate for every therapy that might otherwise be available.

Q3. Sandra's disease progresses, with both hepatic and lung metastases present. She still has normal renal function, so she is started on platinum-based chemotherapy and achieves a partial response after 6 cycles. Which immunotherapy agent(s) would be NCCN-recommended to initiate as maintenance therapy in this patient?

Q3 Answer:

Marcus: Luckily, avelumab was just FDA-approved and added to the NCCN guidelines for this specific indication as maintenance therapy for patients with metastatic urothelial cancer who don't progress after at least 4-6 cycles of platinum-based therapy, so this would fit our patient perfectly. Patients treated with avelumab in this setting had about a 50% increase in their overall survival compared to the standard, which was best supportive care, so it should definitely be a consideration for Sandra if she's willing to undergo therapy at this time.

Laura: The use of avelumab is unique in that it's important for clinicians to realize that it's different from our other checkpoint inhibitors because avelumab requires pre-medication for the first 4 infusions in order to minimize the risk of an infusion-related reaction. Patients receiving avelumab should receive an antihistamine and acetaminophen prior to each of the first 4 infusions, and then as needed for subsequent infusions, should they experience an infusion-related reaction. Now Marcus, these infusion-related reactions occurred in approximately 25% of patients receiving avelumab, so while the risk is only for about a quarter of our patients, it's important to also make sure that you are including this information when you are teaching Sandra about her treatment plan because she may not be aware of the need for pre-medication. She needs to be aware and she needs to be a participant in her care, making sure that the infusion nurse administers those and provides her with those pre-medications for the first 4 infusions.

CASE 3: WILLIAM: PROSTATE CANCER

Case: William, a 75-year-old male presents to his physician complaining of difficulty voiding urine and pain in his lower back. On physical exam, the patient has a prostate mass, and biopsy results indicate necrosis and primary Gleason pattern 5, suggestive of very high-risk disease. A CT of the abdomen and pelvis is performed, as well as a CT of his lumbar spine, both which indicate metastatic spread. He is diagnosed with Stage IV prostate cancer and would like to begin therapy as soon as possible.

Q1. According to NCCN guidelines, what immune checkpoint inhibitor(s) would be appropriate for William as first-line therapy?

Q1 Answer:

Laura: The NCCN guidelines are frequently updated based on results from clinical trial data and drug approvals by the FDA. The most recent version of the NCCN guidelines for prostate cancer were released in May of this year.

Marcus: Laura makes a good point**,** the NCCN guidelines are updated frequently**.** Unfortunately, at this time we still don't have any immune checkpoint inhibitors indicated in the first-line setting for metastatic prostate cancer. Since William never received treatment and is now symptomatic with his lower back pain, the NCCN actually recommends first-line treatment with androgen deprivation therapy either as monotherapy or we can use it in combination with an antiandrogen agent, docetaxel, or using radiation therapy in patients that have a lower volume of metastases. Here's where it comes into play working with other healthcare professionals like Laura to make sure we're reviewing the guidelines and giving the most up-to-date care.

Q2. William is started on androgen deprivation therapy with an LHRH-antagonist, degarelix. After 1 year, he becomes resistant to initial therapy and is started on enzalutamide for his CRPC. Based on current NCCN guidelines, which immune checkpoint inhibitor(s) could be combined with enzalutamide in this setting?

Q2 Answer:

Marcus: Similar to what we saw with the first question, there are still no immune checkpoint inhibitors that are recommended by the NCCN to be used in combination with enzalutamide in this setting. While we did see in cohort C of the KEYNOTE-365 study [Berry 2020] as well as cohorts 4 and 5 of KEYNOTE-199 study [Hoimes 2020] showing promising results when pembrolizumab was combined with enzalutamide, both of those were studied in patients who had progressed on prior antiandrogen therapy. In this case, since William has not received an antiandrogen, these results can't necessarily be extrapolated for his case. Right now, the NCCN doesn't recommend any checkpoint inhibitors at this time.

Laura: If the provider and patient wanted to pursue treatment with an immune checkpoint inhibitor, one consideration could be to see if he qualifies for enrollment in a clinical trial, as the NCCN always recommends clinical trial enrollment when possible. There's an opportunity then for Marcus, for pharmacist, for nurses, and for the team to identify if a clinical trial is available and/or to encourage the patient and her family to investigate potential clinical trial opportunities. The question then becomes where might they go for that information. There are a variety of websites they can go to and obtain that information, but I think one of the easiest and most supportive ways is the advocacy groups. For bladder cancer there is the Bladder Cancer Advocacy Network – also known as BCAN. For this patient, US Too is a prostate cancer group. The Kidney Cancer Association is an excellent resource for patients and loved ones with kidney cancer. Referring them to support groups at any point during their diagnosis and treatment provides them with an additional network that supports us as a multidisciplinary team to help clinical outcomes.

Q3. After an additional year, he is no longer responding to enzalutamide. Based on current NCCN guidelines, what genetic testing should be performed prior to initiating an immune checkpoint inhibitor in this patient?

Q3 Answer:

Marcus: Finally, we get to the role of immune checkpoint inhibitors in prostate cancer. In this case the NCCN recommends pembrolizumab potentially as monotherapy after progressing on enzalutamide. But, importantly, he will need to undergo testing to see if William does in fact have an MSI-high or dMMR tumor status. If after genetic testing William is found to have no mutations in his mismatch repair genes, that would grant him MSI-high or dMMR, then pembrolizumab would not be an option because we have not seen benefit in patients without these mutations.

Laura: If they have a strong desire to seek out immunotherapy options, I would again encourage consideration of a clinical trial. We're seeing more and more trials that are driven based on biomarkers and developing indications for tumor agnostic regimens which are driven based on biomarkers such as MSI-high. For patients with refractory malignancies, there are opportunities to participate in these studies investigating the efficacy of new treatments- including immunotherapy agents. Stay tuned, more to come; these are evolving and coming out on a frequent basis.

CASE 4: IMMUNE-RELATED ADVERSE EVENTS

Case: Lee, a 61-year-old male, has been receiving pembrolizumab plus axitinib for 5 months with mild fatigue, and hypertension controlled with amlodipine 10mg daily and lisinopril 10 mg (added by his nephrologist for HTN and CKD). The patient calls the oncologist office to report multiple episodes of loose stool which started 5 days ago.

Q1. What questions should the oncology provider ask Lee relative to the report of diarrhea for 5 days?

Q1 Answer

Laura: One of the first questions I'd ask Lee is how many bowel movements he's had per day, what is the least number and the most during the past 3 days? Even though he reports diarrhea for 5 days, I don't think he's going to remember the fourth and fifth day; I'm happy if he can remember the past 3 days, which will give me enough of a trend. When we ask Lee that question, his response is that he had a maximum of 6 loose stools in a day, and a minimum of 3. We know that he is having more frequent stools, but we don't truly know that without asking him or looking in the chart as to what his bowel movement pattern per day was prior to starting the pembrolizumab and axitinib. The chart notes were well-documented, which is one of my pearls, to document baseline status – do they have itching, do the have diarrhea, what is their routine bowel pattern. We're able to find out, and the patient confirms, that his normal routine was one bowel movement per day. We know that this is 5 above his baseline. Then we need to ask him what other symptoms are associated with the diarrhea. Is he experiencing fever, chills, abdominal cramping, mucous or any blood in the stools, and is he experiencing any dizziness or light-headedness?

Marcus: Then following up on those questions, Laura, we'd like to ask what have his blood pressure and pulse been like the past 3 days? We're looking to see if maybe there are any indications that he's

becoming hypovolemic from the volume of diarrhea he's having. Seeing if his pulse might be speeding up, if his blood pressure is dipping down, asking if he's had any dietary modifications – he might have had something that irritated his stomach and might be having more diarrhea due to that in part. Then, especially from a pharmacist's perspective, I'd want to know what medications has he tried taken so far. That would also guide us to see how severe the diarrhea is; potentially if he's already been taking over-the-counter medications for the last several days and they haven't helped, that might indicate an even higher level where we might to bring him in and treat at that point.

Laura: You bring up great points, Marcus, as far as the medications and what his blood pressure has been. I think it's important for patients with these drugs to be doing home blood pressure monitoring and maintaining a diary. It's very hard to remember these things otherwise. And as you brought up, asking open-ended questions so that he can tell you what he's been doing rather as opposed to validating what you've been asking.

Q2. What grade is the diarrhea based on CTCAE v.5?

Q2 Answer:

Marcus: Based on his history of having just 1 bowel movement per day at baseline, and now that we've gone up to a maximum of 6 in a day, that would be considered Grade 2 by the common toxicity criteria. Less than 4 we would still consider Grade 1, but now that he's between this 4 and 6 number, above baseline, that would be a Grade 2 toxicity.

Laura: As a research nurse, I definitely use the CTCAE criteria quite a bit. For those that are not familiar with this, the CTCAE criteria is the Common Terminology Criteria for Adverse Events. This is used to consistently define the severity of adverse events or side effects. In the clinical trial setting, it provides standardized criteria for determining to severity of side effects and the protocol-defined rationale and timing for dose modification. Even if individuals are not part of a clinical research team, I would encourage them to use this common toxicity criteria, it's easily accessible online, to standardize the discussions regarding side effects and interventions within their own clinical practice. As we've talked about before, Marcus, with the multidisciplinary discussion, we all need to be talking the same language. If I'm talking about moderate diarrhea, you're going to know that fits the Grade 2 definition according to the CTCAE criteria. So, it helps to streamline the conversation and also ensures that we are all on the same page with defining severity and then recommending interventions and treatment modifications.

Q3. What is the appropriate action to take for the diarrhea?

Q3 Answer:

Laura: Based on the fact that it's Grade 2, we would HOLD the axitinib. Assuming that he received the pembrolizumab at another visit and this is the phone call, the only decision is what do you do with the axitinib. We would hold the axitinib and based upon the previous discussion regarding medication intervention, we would want to make sure that loperamide is started after each loose stool, if it was not previously initiated. If he is using loperamide appropriately, then we have the collaborative discussion with the pharmacist and the rest of the clinical team as to what the next steps are. Marcus also alluded

to his pulse and blood pressure; we need to assess for the potential for dehydration or hypotension, in which case we would want to schedule an urgent office visit, labs, and possibly a visit in the infusion area.

It's important to keep in mind that patients with kidney cancer are already at increased risk for both chronic kidney disease, CKD, and acute kidney injury, AKI, due to both the underlying malignancy and any surgical intervention, especially if they've had a partial or radical nephrectomy. An urgent office visit allows the clinician to check kidney function and electrolytes. IV hydration can then protect kidney function, replace electrolytes, and significantly improve quality of life for the patient. It's amazing how much better patients feel leaving clinic after we've given them a liter of saline, as opposed to how they came in. It may very well be that they arrive in a wheelchair because they're afraid of falling and a family member is afraid they are too weak and they're going to fall, or they're dizzy. They walk out with a bit more spunk simply because we gave them fluids as far as replacement.

Marcus: Laura, you bring up a great point and to emphasize that we need to hold the axitinib at this point because we want to try to judge where this diarrhea is coming from since we're using combination therapy. The axitinib half-life at the upper range is maybe 6 hours, so we expect the drug to mostly clear from the body after 5 half-lives; we're looking at in little over a day we would expect the drug to clear and subsequently the toxicities, too. Sometimes patients think they have to keep taking the medication to keep treating their cancer, but it's important that we don't keep exacerbating that diarrhea. So as you said, Laura, hold the medication and within 2 to 3 days if it's still persistent and it's not really improving with the temporary holding and the addition of loperamide, then as you said, bringing them in for labs, potentially some hydration, and consider if there's the potential for an infectious cause of their diarrhea. If that's negative, then consider it could in fact be immune-mediated, and then thinking about steroids as a first-line option in that case.

Q4. What is the appropriate follow up for the oncology provider based on the diarrhea?

Q4 Answer:

Marcus: Once we give the education that Laura and I mentioned to the patient, we want to follow-up in 24 hours to assess how is the diarrhea, is it still at the same pace, has it gotten any better and their clinical status. As Laura mentioned, having the patient check their blood pressure and then following up to see if it's still stable, has it gotten lower, asking again about the etiology of diarrhea and then considering do we need to modify the dose. If we determine it's solely the axitinib that's contributing to this, because it's resolved right away, then considering do we need to go down on the dose. This is where setting up a work flow at the infusion center comes into play, whether it's going to be the nurse that's following up with the patient and/or the pharmacist following up, and then determining what the right process is for informing the doctor what's going on and figuring out the next steps for the patient.

Laura: That's very true. In our clinical practice, we typically hold the axitinib for 3 days, which is consistent with what you've described as the half-life or 6 doses depending on when the patient calls in, because often times they take their morning dose and then they turn around and call you. So, 3 days would be the equivalent of 6 doses total. If the patient has significant recovery in 3 days, then the axitinib would be restarted at the same dose. But as you alluded to, Marcus, not only if the diarrhea

doesn’t resolve completely or improve, in many cases patients are experiencing multiple treatment-related side effects, or this is a recurrent event, in which case a discussion within the team is very appropriate to consider what is the current dose, should we reduce the dose, should we extend the treatment break, There’ s a lot of collaboration that goes into effectively managing and optimizing clinical outcomes for patients that are receiving these therapies.

Resources

Bladder Cancer Advocacy Network (BCAN): https://bcan.org

The Kidney Cancer Association (KCA): https://www.kidneycancer.org

US Too (prostate cancer): www.ustoo.org

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