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Managing Immune-Related Adverse Events in Metastatic NSCLC

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Bristol Myers Squibb. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology on ReachMD,* and I'm Dr. Charles Turck. Today, I'm joined by Dr. Paul Bunn, Distinguished Professor of Medicine in the Division of Medical Oncology and the James Dudley Chair in Cancer Research at the University of Colorado Anschutz. Together, we'll be talking about how we can recognize and manage immune-related adverse events in metastatic non-small cell lung cancer. Dr. Bunn, welcome to the program.

Dr. Bunn:
I'm happy to be here, Dr. Turck.

Dr. Turck:
Well, to help set the stage, Dr. Bunn, would you tell us how immunotherapy-based combination regimens have reshaped the first-line treatment of metastatic non-small cell lung cancer and where immune-related adverse events fit into the overall risk-benefit conversation?

Dr. Bunn:
Immunotherapy has changed the landscape for all stages and all histologies of lung cancer, including both small cell and non-small cell, except for non-small cell stage one where surgery alone remains the standard. So if all of these patients are receiving immunotherapy, we need to be well aware of the many side effects of immunotherapy, how to manage them, and how that influences the overall treatment of these patients.

Dr. Turck:
Now, with that background in mind, let's zero in on some long-term safety findings. In trials like KEYNOTE-189, CheckMate 9LA, and IMpower150, grade 3 or higher immune-related adverse events occurred in roughly 10 to 30 percent of patients, with higher rates seen in those receiving dual immunotherapy. So what key safety signals should we be paying close attention to?

Dr. Bunn:
So first of all, with chemotherapy, of course, the side effects occur right away and generally peak about 10 days after the treatment. Immunotherapy is generally given for long periods—one to two years in most settings—and immune side effects can occur at any time during the administration of the drugs. It doesn't happen necessarily right in the beginning.

One of the interesting things about immune side effects is, generally, they're most apparent in one organ. One would think that since this is a systemic treatment, it's going everywhere in your body and that if you got side effects, they would occur in multiple organs. Whereas in fact, most of the time, the side effects are in only one organ.

So one of the more common organs affected is the skin, and you would think that the toxicity in the skin would be dermatitis, but there are many forms of immune toxicity in the skin. Recently, I encountered a patient that had these changes in their fingertips. And when we went to see the dermatologist, the dermatologist knew right away that this was an immune side effect, but side effects can occur in any organ—if it's in the colon, it's colitis, or in the lung, it's pneumonitis, and so on. And again, these side effects can occur at any time during the treatment up to two years.

In general, for patients who have grade three or four toxicity in any of the organs, we discontinue the immune treatment and treat with steroids, and generally, that's high-dose steroids, and then those are tapered over one to two months. For patients who have grade three toxicity that have a good response, we generally will restart the treatment and watch carefully for recurrence of side effects, but sometimes, the patients can go back to their standard treatment.

Another interesting thing is that patients who have immune side effects that have grade three severe or grade four and don't reinstitute the immunotherapy frequently stay free of disease for long periods of time, indicating the immune memory can sometimes cure the cancer cells.

The standard is also to stop the treatment at two years. Most of the patients will not have any recurrence after that. The few that do recur after two years can restart and generally there's another response.

Dr. Turck:
Now, clinical trials have structured protocolized follow-up. How might we incorporate a somewhat similar level of vigilance into real-world practice to ensure timely recognition of immune-related toxicities?

Dr. Bunn:
Generally, especially in the beginning, these treatments are given every three weeks, which means the patients are coming in to the clinic or the infusion center every three weeks. And certainly, every three weeks during the administration, a careful review looking for toxicities from these treatments should occur.

Sometimes when the patients are on long-term immunotherapy, the treatments can be doubled in the dose and given every six weeks instead of every three weeks. And again, if this is the case, every six weeks a careful analysis looking for toxicity should occur.

Dr. Turck:
For those just tuning in, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Paul Bunn about managing immune-related toxicities in patients receiving immunotherapy-based combination regimens for metastatic non-small cell lung cancer.

Now, Dr. Bunn, we know that low-grade toxicities can evolve into more serious events. So what early warning signs do we often miss, and what kind of impact can earlier intervention have on a patient's clinical trajectory?

Dr. Bunn:
Well, as I mentioned, looking for toxicity should occur every time the patient comes, and patients should be aware that even between visits if something new should arise, they should call the clinic or the physician and report what's happening. But certainly, just like with chemotherapy toxicity, careful monitoring is incredibly important, and at each visit, there should be a history looking for anything new as well as the physical examination.

Most toxicities, as you just mentioned, when they begin are not grade four, but they generally progress. And so finding them early can save patients from prolonged absence of disease and prolonged steroids. So if one found grade one or two toxicities, obviously you're going to hold the treatment and therefore prevent development of grade three or four toxicities, which can be life-threatening.

Dr. Turck:
And when you're managing immune-related adverse events, what factors help you decide whether to hold therapy, initiate corticosteroids, or escalate to immunosuppressants?

Dr. Bunn:
The severity of the side effects. So if one has minor skin rash, which is grade one, most likely you're going to continue. If you have a severe rash over your entire body, obviously that's going to be grade three or four and you're going to hold the treatment and give steroids. So the tricky thing about immune treatments is one would think since these are given systemically, you would get toxicity in multiple organs. What's interesting is, generally, it's just in one organ.

Now, these patients have lung cancer, and so one of the more difficult toxicities is in the lung: pneumonitis. And frequently when there's pneumonitis, sometimes it's difficult to determine whether there's tumor progression, infection, or toxicity from the treatment. But certainly, a severe inflammation in the lung causing shortness of breath with changes on the CT scan are going to lead to holding the treatment and, in severe cases, treating with high-dose steroids.

Dr. Turck:
Now, before we close, Dr. Bunn, let's take a step back and look at the big picture here. Given everything we've discussed, what should we keep top of mind to maintain efficacy while still prioritizing patient safety when employing immunotherapy-based combination

regimens?

Dr. Bunn:
Well, I think the first thing for everyone to understand is that chemotherapy—while it's a backbone of treatment—does not cure patients. And certainly, for any patient of any histology and any stage, the goal is to cure them. And immunotherapy—while it does not cure the majority of patients—can lead to cure of patients, which is, again, the goal.

So we want to safely administer as much immunotherapy as we can, and as you mentioned, that requires careful scrutiny every three weeks when the patients come in for their treatment and careful monitoring. And also making sure that the patients are aware of potential side effects so that they will call the physician if there's a new toxicity in between visits.

Curative treatment is incredibly important, but monitoring the side effects, which can be life-threatening, is equally important for these patients.

Dr. Turck:
Well, with those final comments in mind, I want to thank my guest, Dr. Paul Bunn, for joining me to share his insights on monitoring and managing immune-related toxicities in metastatic non-small cell lung cancer care. Dr. Bunn, it is great having you on the program.

Dr. Bunn:
Thank you very much. It was great to be here and talk to you.

Announcer:
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