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Reevaluating Platinum Rechallenge in SCLC: Challenging the Status Quo

Announcer:
Welcome to *Project Oncology* on ReachMD, and this episode is sponsored by Jazz Pharmaceuticals. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss platinum rechallenge in small cell lung cancer are Drs. Jacob Sands and Joshua Sabari. Not only is Dr. Sands a fellow ReachMD host, but he's also a thoracic oncologist at the Dana-Farber Cancer Institute in Boston, Massachusetts. Dr. Sands, welcome to the program.

Dr. Sands:
Thanks for having me.

Dr. Turck:
And Dr. Sabari is an Attending Physician in Thoracic Medical Oncology and an Assistant Professor of Medicine at NYU Langone Health in New York City. Dr. Sabari, thanks for being here today.

Dr. Sabari:
Well, thanks for having me. Looking forward to a great discussion.

Dr. Turck:
Now to start us off, Dr. Sands, how do we currently approach platinum rechallenge in the management of patients with small cell lung cancer? And does this strategy have any limitations?

Dr. Sands:
So, this is done differently in different institutions and by different oncologists really. I think broadly we can reference the NCCN guidelines which say that at a greater than six-month chemotherapy-free interval, platinum rechallenge is recommended. On there it also says if greater than three-month chemotherapy-free interval, platinum rechallenge can be considered, and that's more in line with the standard of practice in Europe. I can say in my practice, I'm not really one for platinum rechallenge that much. Certainly, there are some cases where I'd consider that. I think in the cases where we see platinum sensitivity with durable responses, that's not necessarily so indicative of platinum sensitivity alone but rather cytotoxicity susceptibility, and, therefore, other regimens are also more likely to work in these patients than in patients where you don't see much of a benefit from that initial first-line platinum therapy. So with platinum rechallenge, I would not expect that to work as well the second time as it did the first time and so that can go into the decision about platinum rechallenge, but broadly speaking, kind of keeping it on the surface for this first question, greater than six month chemotherapy-free interval, I'd say widely considered varies from practice to practice how much people do that. Greater than three months chemotherapy-free interval common practice in Europe, less common in the US but is per NCCN guidelines something that can be considered.

Dr. Turck:
And moving to you, Dr. Sabari, I wanted to get your own thoughts about guideline recommendations for platinum rechallenge and any limitations they may have.

Dr. Sabari:
Yeah, I agree with Dr. Sands here. The extrapolating from the ovarian cancer population where Carbo-Taxol's a mainstay, you think about platinum sensitivity and what other agents are available at the time of progression, and I think the biology of small cell lung cancer

is quite different, and like Dr. Sands mentioned, you know, greater than 180 days chemotherapy-free interval is the clear NCCN recommendation. The ESMO guidelines, as we mentioned, are quite shorter. Right? In that three month 90-day range. But in my own clinical practice, I think if you have other agents that are available with potentially less cytotoxicity and more activity durability, I tend to think about utilizing other agents in this setting. One of the major things or issues with utilizing platinum doublet again in the rechallenge setting is the toxicity, and I look forward to talking about that.

Dr. Turck:
Well getting to that just a little bit further, Dr. Sabari, what are some of the key obstacles encountered during platinum rechallenge that can contribute to treatment burden and prevent patients from transitioning to a different type of therapy?

Dr. Sabari:
Yeah, so my standard of care in the front-line setting is a platinum doublet with a PD-L1 inhibitor, and most patients are tolerating cycle 1 and cycle 2 relatively well. By cycle 3 and cycle 4, we do see, profound hematologic toxicities neutropenia you know, leukopenia obviously, as well as issues, fatigue, nausea, emesis, and I think here in the US it's very rare or uncommon to utilize a fifth and sixth cycle as our colleagues in Europe commonly do. If you then have a patient who's, you know, completed the 4 cycles and then is on maintenance PD-L1 inhibitor therapy and has recurrence within, you know, a three or six month period, rechallenging with platinum-etoposide again does have significant toxicity. So, I see a twofold increase in neutropenia and neutropenic fever in that patient population. There is also a concern about rechallenge with carboplatin and infusion reaction. So, we do see an increase there as well so critical to premedicate patients with steroids, and I think overall it's just the response rates and the durability of response are far less than what we expect to see in the front-line setting.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Jacob Sands and Dr. Joshua Sabari about platinum rechallenge in small cell lung cancer. Now, with these challenges in mind, let's take a look at key criteria for using an alternate second-line therapy. Dr. Sands, how do you determine whether to switch your patient to this type of therapy?

Dr. Sands:
So, at progression on first-line chemotherapy plus immunotherapy, so as Dr. Sabari said four cycles of carboplatin-etoposide plus either durvalumab or atezolizumab is what I would consider the standard of care for first line and in some of these people we see incredibly durable responses. I've had some where they have progression at a solitary site, and in those cases then I'd consider radiating that site and continuing immunotherapy depending on some of the specifics. I think that's a little outside of the scope of what we're meant to discuss here, but I just need to acknowledge that. Somebody with multiple sites of clearly progressing small cell lung cancer, now we really need to switch therapy. Now, if that's someone who is years in now it's been a very long time since they've had platinum-etoposide, of course, that can be considered as a second line. As I've said that I tend to reach toward some of the other options in the second line, which I'll get to. If it's someone who's had progression really very early on where they're two months out from their chemotherapy of platinum-etoposide, that is a much more challenging scenario, and in that case really platinum-etoposide is not a consideration. And in somebody who's had progression on platinum-etoposide – is like 1 or 2 cycles in and has progression – thankfully that's quite rare, and when that occurs, that is often just a devastatingly terrible scenario with highly resistant small cell. So, I think what I'm going to focus on then within that context is somebody who has progression within months of their platinum-etoposide, and they've got multiple sites of progression, and in that setting, the FDA-approved second-line options would be lurbinectedin as a newer option within the last few years or topotecan, which is a longstanding second-line option. Topotecan is something that really has quite a bit of toxicity.

Dr. Turck:
Staying with you, Dr. Sands, would you share a case with us where you transitioned a patient to a second-line therapy? And what were some of the outcomes you saw?

Dr. Sands:
Well, so speaking about that broadly, I have a guy who was on platinum-etoposide and immunotherapy. He had about six months of chemotherapy-free interval, so kind of around that point at which in the US platinum-etoposide retreatment would be an option went on lurbinectedin as a second-line therapy, and this was a guy who had been quite active. He was somebody, or is somebody, I believe he was in his late sixties, and had been active exercising every day, and he had really a lot of liver disease, and at progression was really slowing down, and I started him on lurbinectedin. He had a beautiful radiographic response to that treatment really quite early. On the first scan two cycles into lurbinectedin had significant reduction, particularly within his liver mets, and he really got back to exercising every day and being active, and now for him, that lasted probably around nine-ish months, I'd say, which I think is a little bit on the longer end. There are certainly patients in the trials that had longer disease control, but as far as that nine-month timeframe, I think is

where we start seeing some decreasing numbers of those with ongoing responses to therapy. But nine months in the second-line setting is really quite meaningful. But on top of that, really getting back to being physically active again and with his normal quality of life. And I'll say, he went on next to one of the T-cell engagers, and again had a really durable response on that, which again just to highlight clinical trials options.

Dr. Turck:
Now before we close, I'd like to get some advice from each of you on how we can help community oncologists tailor treatment to their patients' needs. Dr. Sabari, let's start with you.

Dr. Sabari:
Yeah. So, first and foremost, I think that as we heard today, small cell lung cancer is a highly aggressive disease, and a lot of patients at initial presentation have performance status that is not ideal, ECOG performance status of three or four. Oftentimes, you're meeting these patients in the inpatient setting, and I think, one thing we have to note is that if the performance status is poor, related to their disease, these are patients who will benefit from receiving systemic therapy. Imagine the patient who was playing tennis or now pickleball, right, two to three months ago and now is admitted, that's a different patient and a patient who's been in a wheelchair, on oxygen for two or three years. So, really important to ask your patients where they were, what their functional status was. Get sort of collaborating information from support. And patients do very well in the sense of response, right? Response rates to platinum-etoposide plus a PD-L1 inhibitor in the front-line setting is 70 to 80 percent, and although this disease clearly is not curable, it's treatable, and one really important thing in the community and in our academic settings is engaging with patients and asking them their sort of goals of care and what do they want. If a patient clearly states they don't want systemic therapy and they want to enroll in hospice, I think we need to support them there, but explaining to them that there are good options and good therapies available. So really starting therapy quickly if it's in line with the patient's goals of care. We really need to move this field forward, and again, I echo that more is being done right now in small cell than at any time in history, so really an exciting time for both oncologists in this space, but clearly for patients and for their families.

Dr. Turck:
Thanks so much, Dr. Sabari. And, Dr. Sands, I'll turn to you for the final word.

Dr. Sands:
Well, so much of what Dr. Sabari just said is really important. I mean, just to underline two parts of that, small cell lung cancer is an absolutely terrible diagnosis. I think everybody knows that, and unfortunately maybe emphasizes that too much now, because the other component Dr. Sabari said is that we're making some progress, that there are things going on, and there are options. And at the same time, that discussion with patients that he mentioned and really listening now. Some patients don't want further treatment, and, of course, we listen to them, but oftentimes, they're not aware of the success opportunity that exists. Now, not everybody has a response to therapy in the second line and beyond. Clearly, in the first line, we expect responses, we expect improvement in quality of life with reduction of symptoms from small cell. I think widely in the community, patients are not offered further options, and I only say that because I've seen a number of patients that come to me thinking there's this Hail Mary type of scenario where they've been told there's nothing more and hospice was discussed with them, and when we discuss other even FDA-approved options, that's a surprise to them, and some of that is just, small cell lung cancer is so terrible that oftentimes people kind of expect a sudden decline, a clinical decline, which can happen, but clinical trials are really such an important part of care right now. And I have one patient right now, two years of ongoing disease control on a trial. So, there really are some exciting things happening, and if you don't have trials available at your center, I think it's really important to connect with a local thoracic oncologist to at least know about what trials are available there. Of course, I am always happy to fit people in urgently. People can always reach out to me for the oncologists in the Boston area, or patients that want to travel here. This is really an important part of their care now.

Dr. Turck:
Well, with those pieces of advice in mind, I want to thank my guests, Drs. Jacob Sands and Joshua Sabari, for joining me to take a look at platinum rechallenge and alternate therapies in small cell lung cancer. Dr. Sands, Dr. Sabari, it was great having you both on the program.

Dr. Sands:
Thanks so much.

Dr. Sabari:
Thanks for having me.

Announcer:

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