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Uncovering the Unmet Needs of Relapsing Small Cell Lung Cancer

Announcer:
You're listening to ReachMD, and this episode of *Project Oncology* is sponsored by Jazz Pharmaceuticals. Here's your host, Dr. Matt Birnholz.

Dr. Birnholz:
For patients with small cell lung cancer, based on its highly aggressive characteristics, the question of whether or not a relapse will be the question of whether or not a relapse will be experienced sadly is less a matter of 'if' and more a matter of 'when.' And this leads to complex questions on what to do for patients in these circumstances. Platinum rechallenge therapy has been a consistent go-to in this second and later lines of treatment, but it can come at a heavy cost to quality of life and may have diminished rates of returns for patients with successive rounds. On today's program, we'll dive into the rationales, limitations, and pathways forward in the treatment of relapsing small cell lung cancer.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Matt Birnholz and joining me is none other than Dr. Jacob Sands, a thoracic medical oncologist at the Dana-Farber Cancer Institute and esteemed ReachMD medical oncology host. Dr. Sands, welcome to the program, great to have you on the other side of the table.

Dr. Sands:
Thank you so much. I'm really happy to be on this side and really looking forward to the discussion.

Dr. Birnholz:
So, why don't we start with some background, here, because I understand that there are some recent updates on how small cell lung cancer's origins are understood with its recent classification as a transcription-based tumor. What can you tell us about that?

Dr. Sands:
Yeah, so the genomics of small cell lung cancer are such that the most common mutations we see are p53 and RB1 loss, and these mutations, essentially, what the genes do is essentially take cells that where the DNA is altered and they halt the cell cycle for, to allow time to repair the DNA. And so, essentially, what's happening in small cell lung cancer is you've got genomic mutations that are essentially stopping the brakes from being effective. Now, at the same time, we often see MYC amplification, which is present in about 20 percent of cases and MYC amplification is essentially the gas pedal. So, that's the gas pedal being stuck on. And this is what leads to small cell lung cancer being so often, so rapidly progressive is you've got the brakes not functional and the gas pedal pushed down.

Dr. Birnholz:
And I'd love to compare that to non-small cell lung cancer, which seems to be looked at in a very similar way. We have a number of identified biomarkers that lead to targeted therapies, not so much the case for small cell lung cancer, though. Is that right?

Dr. Sands:
That's right, so in non-small cell lung cancer, this has really been, really one of the biggest advances in the last decade, I'd say in all of cancer care. And within lung cancer, we've identified these various genomic alterations whether it be mutations or fusions, but genomic alterations that we can then effectively target with pills. So, drugs have been developed that then target these cells. And this has led to, in many cases, really exceptional outcomes, the overwhelming majority of patients having a nice response to therapy, generally pretty well-tolerated drugs, as well. So we're really matching up effective and well-tolerated so in non-small cell lung cancer, this has been revolutionary.

Now, in small cell lung cancer, we don't have that. In small cell lung cancer, we have found DLL3 seems to be a real target. Now, that really comes from a drug called Rova-T which is an antibody-drug conjugate that was targeting DLL3. And unfortunately, that really has not been an adopted and effective drug. It really caused quite a bit of toxicity. I don't know if that's still in study at this point but really has been deemed as, kind of, a failed drug at this point. But it did demonstrate that DLL3 is, in fact, a real target as there were patients, certainly, that responded to that therapy, as well. So, DLL3 has been promising. There hasn't yet been anything that has become an effective drug that's targeted to it. But there are multiple drugs in development with ongoing trials for DLL3. That's as close as we can really come. It's not quite the same, that's a surface receptor, it's not really a genomic alteration, like what we see in non-small cell, but that's as close as we can really come to that. We still have a lot of work in small cell.

Dr. Birnholz:
Well, let's use that as a segue to consider the current therapeutic landscape for small cell, what treatment options are currently available for patients in the first line and beyond? And maybe you can tell us where platinum-based regimens fit in, most commonly?

Dr. Sands:
Yeah, so, small cell lung cancer is really, kind of, a case of two scenarios. On the one hand, at initial diagnosis with platinum-based therapy, which is really platinum etoposide, for the most part, in the U.S. platinum irinotecan there within Japan there's a study that shows that to be effective. We see a little bit of a difference in outcomes between the populations. But platinum-based therapy in the first-line setting, very effective, often rapidly effective really is like a wonder drug for patients that are initially diagnosed, symptoms quickly improve to resolve even patients get back to their lives. At the same time, at progression, it's a totally different scenario. And so, at the time that the cancer then progresses in the second-line setting, it is often very resistant there aren't a lot of incredibly effective therapies. There are an array of treatment options, but very limited approved options. So, I'm gonna focus a little bit on that second-line setting, because in the first line, the treatment's effective, it's pretty clear, it's platinum-based therapy, adding in immunotherapy, at this point, which we can talk a little bit about, as well.

First-line therapy, really clear. Second-line, now, we have multiple options if you look at NCCN guidelines, for example, but as far as FDA-approved therapies, there are really only a couple. Topotecan has really been the historical approved second-line option although that is limited to patients who have a chemotherapy-free interval, which is the time since completing the platinum etoposide therapy to when they have progression. With topotecan PO approved for after 45 days, is topotecan IV approved after 60 days chemotherapy-free interval. But I'd say topotecan is not a widely used drug, or at least certainly not widely used as what you'd expect, given that it was the clear approved second-line option. And I think that it's largely because it's not overwhelmingly effective, and the toxicities are real. And so, if you have a drug that doesn't end up working for somebody and it causes toxicities, as they have worsening disease you see that a handful of times, and you really don't wanna cause that to people. So, topotecan is used but not as widely as maybe you'd expect it to be.

Lurbinectedin, a recently approved second-line option, which we can talk about more but also now a newer option that is being utilized, as well. And then if the chemotherapy-free interval is greater than six months, then rechallenge with platinum etoposide is considered an option. Some would argue three months, but more commonly six months chemotherapy-free interval. And I'll admit, I don't tend to use that as much as others and really that stems from the fact that we don't see the effects to be as good the second time around. So, if you get a chemotherapy-free interval of six months, well, then on the second time around, I would expect a chemotherapy-free interval to be less, maybe around three-ish months, which is not to say it's not meaningful, it is but getting the chemotherapy, it does affect people's lives, they lose their hair, which for some people it matters a lot and for others, it doesn't matter at all. Less energy, less appetite, I'd expect for about a week out of each three-week cycle for four cycles. So, it does affect people's lives and the effects of it, I don't expect to be as much the second time around as I do the first.

So, as for each individual that would be an option really depending on how they tolerated it the first time around. If they really cruised through, no issues, then that becomes a more appealing option than if they had any issues with it the first time around. Beyond that, there are really an array of other possibilities based upon guidelines such as single-agent paclitaxel, single-agent irinotecan temozolomide is a bit intriguing, particularly those who have CNS disease 'cause it has good CNS penetration. And that's, kind of, the list of different possibilities.

Dr. Birnholz:
Dr. Sands, do you find that colleagues in your specialty often turn towards platinum rechallenge therapy not instinctively, but quicker and that the progression from rechallenge to Hospice care becomes progressively tighter as one goes into second and third line and beyond treatment phases?

Dr. Sands:
I think that's true. We certainly, so in a second-line setting for years really, all that there was, for the most part, was the platinum

rechallenge and topotecan. And some of these other drugs I've mentioned have very limited data, although our guidelines have potential. But, yes I think many clinicians have decided either platinum rechallenge or topotecan or in many cases, I think patients are often put on Hospice due to just the perspective in the second-line setting and beyond that, it is a more resistant disease and so there's really, I think, less hope that people would, discuss with their patients. But I'll say, that's a sticking point for me because as somebody that really focuses on small cell treatment I see patients that were put on Hospice by their local oncologists and they come to me as this, kind of, last-ditch, hail-Mary effort in their minds, of anything that might be out there. And in some cases, I'm putting them on drugs that have been around for a long time, and they have a nice response to therapy and it's effective and working for them. So, I do think that especially when you talk about in community setting where you have oncologists that are treating everything and then maybe they just see a handful of small cell lung cancer cases at second-line and beyond where it's really challenging in that I think patient's sometimes end up on hospice care when they do have treatment options. So, that paradigm you're describing, yes, exists, I don't think that that is necessarily how it should be, but in think historically, we've certainly seen that.

Dr. Birnholz:
Well, for those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Matt Birnholz, and I'm speaking with Dr. Jacob Sands about therapeutic challenges and pathways forward in the setting of relapsing small cell lung cancer.

So, Dr. Sands, coming back to what we were just talking about, you spoke to the NCCN guidelines and I just want to get a sense from you whether the current guidelines provide clear directives for second-line therapies and beyond, or are there some ambiguities there?

Dr. Sands:
My appreciation for the challenges of creating guidelines has really been strengthened by my being on the NCCN guidelines committee and being a part of those discussions and recognizing that you know when you're creating guidelines you're creating this overall structure from which you're, you're providing, saying that clinicians can choose these different options. And we sometimes have debates saying, 'Well, you know, this one thing that we're talking about, what about this other, kind of, specific scenario?' or 'Should it really be recommended if such-and-such?' and the challenges that we're talking about broad recommendations that we're describing as reasonable options while recognizing that each patient needs to be individually evaluated as to what's the right thing for that person. And so, guidelines, I think should be seen as just a very broad statement. And essentially saying to the medical community, these are all reasonable options whether that be insurance companies, hey if a physician is prescribing such-and-such a drug, we think that that is a very reasonable thing for them to do and that that makes sense. And so, that's a little bit different than the FDA-approved regimens. And so, to that point, we do see on the NCCN guidelines there are multiple drugs on there that are considered very reasonable options and argued by many that are not explicitly FDA approved.

So, it is gonna be a broad statement that isn't necessarily something that's relevant for every individual patient but should be taken broadly.

Dr. Birnholz:
Well, that's a great way to frame my next question, which is going from broad into the specific, the individual care paradigms that you speak to that you practice so faithfully, and I'm interested in the key factors that you think oncologists should be weighing when deciding on treatment options such as platinum rechallenge therapy in the event of relapsing small cell lung cancer. You talked about elements of patient preferences, and do they actually want to undergo this again, and sensitivities and tolerably, can you just speak to the factors that you weigh?

Dr. Sands:
Yeah, so at the time of progression and really the biggest factor is what was the chemotherapy-free interval? If the chemotherapy-free interval was greater than six months, then rechallenge with platinum-based therapy is certainly considered a reasonable and guidelines-approved option. Other options are topotecan which, as I've said, I'm not as enthusiastic about, but it is an FDA-approved and a clear potential option. And then lurbinectedin which, as a single agent from the basket trial led to accelerated approval and is generally well-tolerated and is an option that I've increasingly utilized.

As far as how I decide on those, I have personally more increasingly used lurbinectedin, as I've seen, good responses to therapy and generally pretty well-tolerated. I will say that in the basket trial they reported a 7 percent grade 3 fatigue. And you never really know what to do with that in a single-arm study because of course, progressive small cell lung cancer would cause fatigue and so, I was a little skeptical as to maybe that was in part from the small cell. But I have found that there are some patients that really develop pretty significant fatigue. And so, that is something to be aware of. That being said, there was a patient that I had to stop the drug, actually, because of fatigue. But he had an ongoing four more months of disease control, even off of the drug. And so, it has been nice to see those responses.

I guess to come back to the specific question as to how to choose I'm seeing lurbinectedin, I'm, kind of, focusing on that because by and

large that is what I have been using as my second-line therapy. If there is a greater than six-month chemotherapy-free interval, that is also an option. I think it then, it really comes down to what patients have, how they tolerated that first line, and whether or not losing their hair is really something that, that bothers them because that is, something that happens with, with platinum etoposide.

And then topotecan as I've said I'm not really a big proponent on that. I haven't found as much benefit from that, so those are, kind of, some broad statements about choosing therapies.

Dr. Birnholz:
So, my last question for you, then, Dr. Sands, just given everything we've covered, what counseling methods do you think we should prioritize with these patients to better assess the best treatment course moving forward for each of them?

Dr. Sands:
Well, it's a discussion with a patient, certainly. I mean, of course, that's a classic answer, although I do think we really need to guide them. It's not just telling them, 'Hey, here's what it is, choose' but really helping them in that decision. And it's gonna come down to, for them, what really matters. I've mentioned for example losing hair, I think for some patients that is just overwhelmingly something they would prefer not to. And in some cases I'll counsel them around that; we'll, kind of, dive into why losing hair matters so much to them. I think in some cases, it's really that in their minds, what they picture for someone sick with cancer is someone without hair. But that's, sometimes we can, kind of, think about that in a different way and so that's something I'll explore with patients where it might be meaningful for them. In other cases, patients cruised through their platinum etoposide and they don't have much worry about that would be an area of discussion.

I think what it comes down to for most patients though, is they really stress that they want quality of life. They want to be able to carry on with their lives in the best way possible. And so, having a treatment that's not going to cause them a lot of side effects, is what they prefer.

There really are an array of different options out there. And I guess what I would stress is that if someone is in a second-line setting with progressive disease but a reasonable functional status, I would really encourage clinicians out there to discuss different treatment options with their patients. Because with a reasonable functional status who wants therapy there really are options for these people. And so, I think they should be offered those.

Dr. Birnholz:
That's a fantastic closing thought, Dr. Sands. I could keep you here for much longer, but I do realize and recognize that you're busy, so are our listeners, so we'll cap it there. I very much want to thank my guest, Dr. Jacob Sands for joining me to discuss treatment challenges and best practice recommendations for relapsing small cell lung cancer. Dr. Sands, it was great having you on the program. Thanks, so much.

Dr. Sands:
It's so much fun. Thank you.

Announcer Close
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