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Evolving epNEC Care: From Default Regimens to Precision-Driven Strategies

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Boehringer Ingelheim Pharmaceuticals, Inc. Here's your host, Dr. Alexandria May.

Dr. May:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and joining me to discuss the evolving management of extrapulmonary neuroendocrine carcinoma, or epNEC for short, is Dr. Chandrikha Chandrasekharan. She's a Clinical Associate Professor in the Division of GI Medical Oncology at the University of Texas MD Anderson Cancer Center in Houston.

Dr. Chandrasekharan, thanks for being here today.

Dr. Chandrasekharan:
Thank you, Dr. May, for inviting me to give my thoughts on this excellent and important topic.

Dr. May:
To help set the stage for us, Dr. Chandrasekharan, how would you characterize the current treatment landscape for epNEC across primary sites like GI, GU, and gynecologic origins, and where do you see the most pressing unmet needs?

Dr. Chandrasekharan:
I think at this time, most of what we do in extrapulmonary neuroendocrine carcinoma, or epNECs as we call them altogether, is really based on all borrowed teachings from small cell lung cancer. So our default regimen has for decades just been starting with a platinum etoposide regardless of whether it's a GI origin neuroendocrine carcinoma or gynecological or other origins.

I think we've really come a long way. The past few years have been really exciting in our understanding of factors beyond platinum and targets beyond platinum. I think there's still a lot of unmet needs, especially because I think we still continue to lump them all together in one group, and that may not be the right way.

And I think even as emerging targets like DLL3 and SEZ6 and others are coming up, there could be nuances between the site of origin, in terms of response, and in terms of the tumor's signature. I think that's the biggest unmet need and the future direction of the field.

Dr. May:
Now, we've been seeing more attention around biomarker-informed approaches. Beyond the markers that you're likely already ordering, like MSI, TMB, and PD-L1, how do you see molecular profiling evolving, and what role might it play in shaping our understanding of epNEC biology and guiding future treatment strategies?

Dr. Chandrasekharan:
I think the first step I would like to emphasize is actually utilizing the existing biomarkers. There's still a lot of times I see patients who did not have sequencing done, and then when the disease is progressing, we are in a rush to get these results to look at options. So uptake of existing biomarkers is still an issue.

Also, on the genetic mutation level, with the existing platforms, we often see TP53 mutation or RB loss, which is defining for many of these extrapulmonary neuroendocrine carcinomas. But based on the site of origin, there may be other markers that we can still target. So, for example, colorectal neuroendocrine carcinomas may have a BRAF mutation, just like a colorectal cancer. And there's a possibility or opportunity to use BRAF-directed therapies in these patients. In the same way, KRAS mutations can be found in colorectal or pancreas NECs, and again, they have excellent drugs that are now evolving in clinical trials to use as well.

Now, going beyond the mutational landscape, I think the field is moving towards targets and transcriptional factors like TTF-1 or SEZ6. I think we are probably a little bit further away from using it in primetime just because some of these assays are not widely available. Many labs may not have a validated assay to use, but certainly, there are academic neuroendocrine cancer centers that are already doing DLL3 assays, which pathologists can reach out to and test ahead of time.

I think the other part that is unclear is the cutoffs of when certain drugs may be useful or when certain trials may take patients. I think all this will likely iron out in the next few years, and hopefully it'll become more widely available for use.

Dr. May:
Let's focus specifically on DLL3-directed strategies for a moment. Some target high-expression populations in later-line settings, while others target broader DLL3-positive populations earlier in the disease course. Can you walk us through those differences and what they might mean for patient selection?

Dr. Chandrasekharan:
I think the story of DLL3 is still evolving. The only drug currently available is tarlatamab, which is approved for extensive small cell lung cancer. I think also it's important to recognize that when we find a mode, we come up with multiple tools to back the mode. So there's DLL3 antibody-drug conjugates that are undergoing clinical trials. There are, bispecific T-cell engagers, basically attaching one place to the DLL3 and another to an immune activation arm. And there's also trispecific DLL3 drugs that have improved upon the pharmacokinetic profile maybe in some way, or the immune engagement has improved or has been modified in a way to be a more potent drug.

So with all these different drugs, I think the cutoff, so to speak, for a good number of expression is also definitely going to change. As of what we know right now, certainly, for at least the bispecific antibody drugs, in some of the trials that have been reported, the higher expression of DLL3—defined as greater than or equal to 50 percent over the tumor slash cytoplasmic membrane—that has definitely been linked to a better response to these drugs. But we have to realize, borrowing also again from other cancers, antibody-drug conjugates may act a little bit differently. They may need even lesser DLL3 expression on the tumor for the drug to get into the nucleus and release the payload there. So I think some of the ongoing trials, for example, with DLL3 ADCs, do not have a specific cutoff. I think definitely are going to look into the expression levels and therapeutic responses and efficacy, but I think that may also change.

The other question you had was about the line of therapy. I think, again, it's another area of excitement because the good thing about these, especially the bispecific engagers, is because they're more immune mediating drugs, they could be combined even with traditional cytotoxicity, hopefully without any additional side effects. So certainly there are ongoing trials, especially in combination with the traditional platinum etoposide already. Could there be a time where we actually don't talk about platinum etoposide in the future? What if we combine two other exciting targets that are over expressed, both in ADC or bispecific antibody, and actually compare it to platinum etoposide? I think we could be in that future very soon.

Dr. May:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Dr. Chandrikha Chandrasekharan about advancements in extrapulmonary neuroendocrine carcinoma care.

So, Dr. Chandrasekharan, given the rarity and aggressiveness of epNEC, when should we start thinking about clinical trial referral, including referral to academic or NCI-designated centers when local options are limited? And how do you approach these conversations with patients?

Dr. Chandrasekharan:
I think the ground reality is important to discuss when you come to this cancer. As we discussed, these are very sick patients, often presenting with a very quick clinical decline in liver metastasis. So certainly, depending on where the patient is located and how they're doing, ideally, we would like, especially with the first-line clinical trials, patients to be referred as soon as they're diagnosed. I think there's always going to be some gap between what we hope for and what happens because of the nature of the disease.

But it's important, I think, to start referring them for the second-line trials even in the beginning, because we all know when these patients have disease progression after the first round of platinum etoposide, it's very quick. So even if we did not have the opportunity to do this because of clinical reasons in the very first diagnosis time, we're starting a referral for a potential clinical trial, especially in the patients who are interested, able, and fit, right away for after the second line starts the day they were diagnosed. I think it's really important in this cancer to have plan A, plan B, and plan C as you're planning plan A.

What's good about some of the first-line clinical trials as they're being designed is they do have this in mind, and they do allow for the first dose of chemotherapy, for example, to be administered so the patients can stabilize a little bit and then hopefully get onto an

exciting drug target. So I think that's also lobbying for more patients to be in trials and benefit from these drugs, hopefully.

Dr. May:
As a follow up to that, in a community setting where NEC-specific tumor boards may not always be available, how do you approach patient selection and multidisciplinary coordination when referring to clinical trials to make sure appropriate patients don't miss potential opportunities?

Dr. Chandrasekharan:
I think the challenge in the community, both for the patient or for the oncology team managing them, is to get the patient to a trial. I'm sure there are many hurdles that happen, and I think it has to be a collaborative effort. And I think a lot of work being done by patient advocacy groups increasing awareness of this is the right direction. For example, even as an academic oncologist, I think it's also important for me to engage with non-trial sites to be able to have this referral base to benefit the patient.

And I think as a broader picture, decentralizing trials—this goes beyond the extrapulmonary NECs, but it's a topic dear to my heart. How do we make trials more accessible to maybe smaller communities or rural oncologists? And I think the NCI mechanisms for running some of these trials are great examples, and it is possible to run trials even in extrapulmonary neuroendocrine carcinoma. And a great example I can reference is the SWOG S2012 trial, which is looking at the combination of immunotherapy and chemotherapy in this patient population. And as a SWOG study, it's accessible to more patients in the community, even in rural or urban setups—across the board. And I think going for the decentralized approach is one great way to ensure that patients have access.

Dr. May:
Before we wrap up our discussion, what guidance would you offer to clinicians who are trying to navigate evolving care options while responsibly considering investigational therapies?

Dr. Chandrasekharan:
Just like the information is evolving, there are also amazing tools that are evolving too, whether these are decision-making tools that some places may have or practice guidelines. For example, if you see a breast cancer patient, by default, you have to get estrogen receptor-positive status. So I think such default practice patterns will likely evolve with the help of AI or other tools that are part of the clinic where you see a patient with extrapulmonary neuroendocrine carcinoma. Hopefully, there's a prompt that you're ordering, at the very minimum, existing biomarkers with existing drugs. Hopefully it is able to also prompt NGS testing, and at some point when DLL3 or other markers are more widely available, also test for those. Also, tools can match up patient to the trials that are available to them and the nearest site.

So even though there are some platforms and online resources that exist, I think there's a lot of inadequacies, and how we can make it happen in a very short span of time could be a good place to focus.

Dr. May:
That's a great comment for us to think on as we come to the end of today's program. I'd like to thank my guest, Dr. Chandrikha Chandrasekharan, for joining me to discuss how the treatment landscape for extrapulmonary neuroendocrine carcinoma is evolving.

Dr. Chandrasekharan, it was great having you on the program.

Dr. Chandrasekharan:
Thanks, Dr. May. I appreciate the opportunity.

Announcer:
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