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Understanding Extensive-Stage Small Cell Lung Cancer: Advancements and Ongoing Challenges

Announcer:
You're listening to *Deep Breaths: Updates from CHEST* on ReachMD. This program is produced in partnership with the American College of Chest Physicians and is sponsored by AstraZeneca. And now, here's your host, Dr. Gerard Silvestri.

Dr. Silvestri:
This is *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Gerard Silvestri, a pulmonologist and the Hillenbrand Professor of Thoracic Oncology at the Medical University of South Carolina. Joining me to discuss recent developments and ongoing challenges in extensive stage small cell lung cancer are Drs. Adam Fox, Mariam Alexander, and Anurag Singh.

Dr. Fox is a pulmonologist and Assistant Professor of Medicine at the Medical University of South Carolina, in Charleston. Dr. Fox, welcome to the program.

Dr. Fox:
Thank you so much for having me.

Dr. Silvestri:
And also joining us is Dr. Anurag Singh, who's a Professor of Radiation Oncology and the Director of Radiation Research at the Roswell Park Cancer Center in Buffalo, New York. Thank you, Anu, for joining us.

Dr. Singh:
Thank you for having me.

Dr. Silvestri:
And last but certainly not least, we have Dr. Alexander, who's a medical oncologist and Assistant Professor of Medicine at the Medical University of South Carolina. Dr. Alexander, it's great to have you here as well.

Dr. Alexander:
Thank you so much for having you, Gerard.

Dr. Silvestri:
Well, let's dive right in, starting with you, Adam. Given how aggressive small cell lung cancer is, are there any clinical features that can help us identify it early?

Dr. Fox:
Yeah, absolutely. Unfortunately, early detection of small cell lung cancer remains problematic. So, for instance, if we estimate the doubling time for a non-small cell lung cancer to be around 350 days, that time frame fits pretty nicely around an annual lung cancer screening CT, and so the pace of that disease could be picked up year to year. In contrast, in small cell lung cancer, there's some estimates that the doubling time is about 50 days, so in that year, your tumor could double six or seven times. So we don't have a great screening test, and it's difficult to detect early.

There are a few clinical features, however, that can help clue you in once you have a suspicion image. The first is there's a big association with tobacco use. Most—almost all—patients with small cell lung cancer have a history of tobacco use. And then there's some radiographic features. These are usually large tumors, usually central, very close to the proximal airways. Often, they present in the later extensive, or at least a stage in which many mediastinal lymph nodes are involved in being quite enlarged at diagnosis. And if

you do have more than one image, they do grow quite quickly, so a quickly growing tumor should pique everyone's interest. This needs urgency. But you should also, in the back of your mind, think this is acting like it could be small cell lung cancer. That should really set off alarm bells.

A final note is that anyone with a suspected paraneoplastic syndrome accompanying an image that's suspicious for lung cancer, a nodule, a mass, or mediastinal adenopathy, that should clue you in that this might be small cell lung cancer. It is the most common variety of lung cancers to be associated with paraneoplastic syndromes. And for presentation, think neurologic syndromes. The most symptoms, the most common, would be SIADH with hyponatremia, and the resulting neurologic and other problems, and then there's the myasthenic-type syndromes with muscle weakness.

So those are the things I think about when I think of clues for small cell lung cancer.

Dr. Silvestri:
Yeah, I would throw in Lambert-Eaton syndrome. And the only paraneoplastic syndrome that doesn't seem to be associated as much with small cell lung cancer is hypercalcemia, which is more commonly seen with squamous cell lung cancer. Thank you for that quick intro into what small cell might look like.

Turning to you, Dr. Singh, with such limited survival rates in extensive stage disease, how can we help both patients and teams stay engaged in their care?

Dr. Singh:
Well, the first thing to note is we have a tremendous number of large, randomized trials ongoing in small cell. In fact, it's the most that I have seen in 30 years. And what we need to do is stay engaged with what's coming from those studies.

Dr. Silvestri:
Yeah, one way that try to get people to stay engaged is that, even though the survival might not be outstanding, you can actually get really improved and very quick improvements in both quality of life and control of symptoms with the initial therapies for small cell lung cancer.

So, turning to you, Dr. Alexander, if we look towards new therapeutic strategies, what's in the pipeline for patients who progress after first-line chemotherapy and immunotherapy? And do you care to talk through what Dr. Singh just mentioned about what he's thinking around this disease?

Dr. Alexander:
Yeah. I agree with Dr. Singh. It is a great time to be in small cell lung cancer research. It is an exciting time. We had a recent approval of a drug called tarlatamab in May 2024, which is a bispecific T-cell engager essentially forcing the immune system to be in proximity to the small cell lung cancer cell. So in the pivotal trial DeLLphi-301, there was a response rate of up to 40 percent in patients who had progressed on multiple earlier therapies, including immunotherapy. And the majority of these responses lasted well more than six months—I had a patient at a year—and a median overall survival of more than 14 months. That is really unprecedented for small cell lung cancer after failure of these frontline chemoimmunotherapy treatments.

And tarlatamab is even effective in the brain, with more than 30 percent actually experiencing shrinkage of their brain mets and more than 87 percent of patients experiencing stable intracranial disease. The drug arm has some unique side effects which will need close monitoring, such as cytokine release syndrome and neurotoxicity, during the first month of treatment. But in general, it has a good quality of life.

We also have several antibody drug conjugates that act as smart missiles, delivering chemotherapy in a very targeted way. Several ADCs, or antibody drug conjugates, targeting proteins such as DLL3, B7H3, SEZ6 and Trop2 have been very promising. Some of these compounds are moving quite quickly through the phases of study, with a B7H3 compound called IDXd having a response rate of more than 50 percent and benefits in the brain.

Traditionally, we have used chemotherapy, such as lurbinectedin and topotecan, for patients who have progressed on frontline chemo and immunotherapy. So it is nice to see some new ways to target small cell lung cancer that is showing promise, and it appears that some of these agents will significantly prolong life in patients. So, it is an exciting time.

Dr. Silvestri:
Yeah. So tell me a little bit about the quality of life, because I do have physicians in the pulmonary world who don't even refer for treatment for extensive stage small cell because the outcomes are not great. Can you tell me about why it's important to at least see a medical oncologist and refer for this disease? And what the effects of at least first-line chemo and chemoimmunotherapy might have on

quality of life?

Dr. Alexander:
Yeah. So it is important for patients to at least have these options. We have patients who would have progressed without any treatment very quickly—within days to weeks—and not have received any treatment if they hadn't met a medical oncologist. And several of these patients are living more than five or six years and having really good quality of life.

With tarlatamab, which is the bispecific T-cell-engager—I had a patient after several lines of chemo and immunotherapy who lived almost a year after that and had a really good quality of life because it is not chemo. And so it is certainly important for patients to at least be given these options, especially because these new drugs have lower side effects.

Dr. Silvestri:
Thank you. Thank you for that answer. For those just tuning in, you're listening to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Gerard Silvestri, and I'm speaking with Drs. Adam Fox, Anu Singh and Mariam Alexander about the evolving treatment landscape of extensive stage small cell lung cancer.

So if we continue to look towards the future of patient care, Dr. Alexander, are we any closer to being able to use predictive biomarkers to help personalize treatment the same way we do in non-small cell lung cancer?

Dr. Alexander:
So identifying effective biomarkers for small cell cancer has been quite challenging. It's because small cell lung cancer has a high mutation rate, so it doesn't lend itself to mutation-driven biomarkers. So researchers are focused on expression-based biomarkers, such as transcriptome and proteomic profiles, and this makes it quite tough to implement in the clinic.

In terms of expression profiles, there are four categories that include major neuroendocrine subtypes and immune gene signatures, which make it feel like we're dealing with four different cancers. But these subtypes have not been validated in prospective clinical trials yet.

When traditional biomarkers of immunotherapy response, such as PD-L1 expression—which we use every day in non-small cell lung cancer—were actually looked at in the pivotal CASPIAN and IMpower-133 trial that led to the approval of immunotherapy for extensive stage small cell lung cancer, the PD-L1 expression was actually not found to correlate to the overall survival benefit of adding immunotherapy to chemotherapy. So these subtypes, based on transcription factors, may become more important in the future to predict response to therapy, but we'll have to wait and see.

I do want to mention that there is one biomarker that people may have heard about called Schlafen 11, which did predict some response to a PARP inhibitor. So those worked in the DNA repair pathway in combination with immunotherapy. But so far, the benefit was marginal, so it was more of a proof of principle study. So, all in all, a lot more research is required here.

Dr. Silvestri:
In non-small cell lung cancer, Adam, we've been pushing our pulmonary community to make sure at the time of diagnosis, we're getting enough tissue to be sent for mutational analysis so that we can direct care with targeted therapies. How is precision oncology reshaping your role in small cell lung cancer? And at the time of diagnosis, if you have a rapid on-site evaluation and they say, "This looks like small cell," should we just walk away and go, "Okay, we got it," or should we do anything else?

Dr. Fox:
Well, I will say that there is still reason to get more tissue to build that cell block if you're doing fine needle aspiration or otherwise. Oftentimes, our pathologists and oncology team would like to run some more stains to help confirm that diagnosis. It's often these neuroendocrine tumors that need a little extra work to really be sure about the diagnosis.

But like we just heard from Dr. Alexander, at this time, the treatments are not so precise. So routine biomarker testing is not currently needed, and like you said, in contrast in non-small cell lung cancer, in which they are critical and growing, even more so critical across all stages of non-small cell lung cancer.

So for me, the big change is that immunotherapy is the first new therapy that's making any difference in outcomes for small cell lung cancer, and so I'm looking for potential contraindications to immunotherapy, such as an undiagnosed and/or uncontrolled autoimmune disease, or something that comes up a lot in our tumor boards, pulmonary fibrosis. There's some different risks for pneumonitis amongst patients with pulmonary fibrosis.

There are other therapies in development, and while none of these are biomarker-driven at the time, remember we deployed EGFR inhibitors before we knew that we should be sequencing for mutations in EGFR. That came after the fact. And so as we see more

development and research in this area, people will be looking for biomarkers to help choose between these different treatments.

Dr. Silvestri:
Mariam, I'll throw it back to you. Do you think in one, two, three, or five years, we'll be doing a panel at the time of diagnosis in patients with small cell lung cancer?

Dr. Alexander:
So I don't see us doing the same type of panel as in non-small cell lung cancer where we're looking at specific DNA changes, but if we're trying to run these big transcriptome and proteomic panels to find the exact subtype of the small cell lung cancer, we're going to need a lot more tissue. So, as a medical oncologist, the more tissue the better because if I, in a year or two, have to go back to the path lab and ask for more tissue to run a specific test it, it would just be nice to have that tissue at least prior to the patient having received multiple lines of treatment.

I do want to mention about transformed small cell lung cancer, which is where EGFR cancer can transform into small cell lung cancer. We don't see that as much in the eastern population, in the de novo, like where the patients present to us directly with small cell lung cancer. We usually see them where they initially had non-small cell lung cancer and EGFR mutations and then transform to small cell. But in the Asian population, that is more prevalent. You can see a small cell lung cancer patient that may have started with an EGFR mutation.

So in those patients, there is some research going into adding targeted therapy in addition to chemotherapy. So having maybe a never-smoking history or things like that and having small cell lung cancer, we would want to run the full molecular panel that we normally run for non-small cell lung cancer.

Dr. Silvestri:
I think the take-home from both of you, which I would ask my pulmonary community to consider is, the more tissue, the better. If you're doing EBUS, which is the common way to diagnose lung cancer, it's not just three passes—it's more like six passes now to be put in for cell blocks so that we have enough to treat our patients appropriately.

And as these insights bring us to the end of today's program, Dr. Singh, I have a question for you. As systemic therapy evolves, how can we determine whether consolidated thoracic radiation—something we don't normally do for extensive stage disease like we do for limited stage—is right for a patient with extensive stage small cell lung cancer?

Dr. Singh:
Well, first of all, you're absolutely right that we don't often do it except in select circumstances. So I think it comes back down to a multidisciplinary tumor board discussion where you have to look at the alternative treatment strategies. So, for instance, does Dr. Alexander have another hot agent or another trial to offer the patient after first-line therapy? And how was the response to the first-line therapy? So if they had a complete response, then it's a different discussion than if they had a near-complete response where there's a larger tumor that failed to completely respond, and you may be more inclined to do consolidated radiation prior to going on to other therapies.

So there's that aspect of things, and then there's balancing the toxicities. There's the therapeutic toxicities as well as the time toxicities. For instance, if you're planning on doing immunotherapy or something that has a risk of pneumonitis in a prior radiated field, you're going to need to consider that. And that's where a truly multidisciplinary discussion with all the patient's options have to come into focus.

As a general rule, as systemic therapy improves, I think that we can expect the local therapies will have more and more of a role as has happened with non-small cell lung cancer in the advanced setting.

Dr. Silvestri:
That's awesome. So I'm going to throw out a hypothetical patient. Younger patient, great response, complete response to first-line chemotherapy. You're going to have that discussion. Is that the kind of patient you'd like to see?

Dr. Singh:
Yeah, absolutely. So in that setting, the first question has to be, are you eligible for a trial and are you interested in it? If you are eligible. And if not, then did you have an area that is at high risk for relapse and merits consolidation? And what are the risks of treatment in that area?

So as Adam pointed out, these often tend to be central. Now, you're radiating heart, you're radiating lung, and the question becomes, what are the long-term consequences of that, and what are the additional therapies that the patient is eligible for? And again, it has to be a give-and-take with the patient about what they value and what's important to them.

Dr. Silvestri:
Well, great. Thank you so much. I want to thank my guests, Drs. Adam Fox, Mariam Alexander and Anu Singh, for sharing their perspectives on how we can better care for patients with extensive stage small cell lung cancer. Dr. Fox, Dr. Alexander and Dr. Singh, thank you so much for being here.

Dr. Fox:
Thank you so much for having me.

Dr. Alexander:
Thanks for having me. It was a good discussion.

Dr. Singh:
Great discussion. Thank you.

Announcer:
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