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Pulmonary Toxicities Related to Cancer Treatment

Announcer:
You're listening to *Deep Breaths: Updates from CHEST* on ReachMD. The following episode is part of a four-part educational campaign brought to you by CHEST in collaboration with AstraZeneca.

Here's your host, Dr. Gerard Silvestri, Hillenbrand Professor of Thoracic Oncology of the Division of Pulmonary and Critical Care Medicine at the University of South Carolina.

Dr. Sylvestri:
About 10% of all cancer patients develop treatment-related pulmonary complications. But for lung cancer patients, that risk is even greater. What are some of these complications, and how can we help our patients manage them?

Welcome to *Deep Breaths, Updates from CHEST* on ReachMD. I'm Dr. Gerard Sylvestri and joining me today to talk about the management of pulmonary complications from lung cancer treatment is Dr. Lynn Tanoue, Professor of Medicine, Vice-Chair for Clinical Affairs in the section of pulmonary critical care and sleep medicine, and the Director of the screening program at Yale Cancer Center in New Haven, Connecticut. Dr. Tanoue, welcome to the program.

Dr. Tanoue:
Thanks for having me.

Dr. Sylvestri:
Let's dive right in, Dr. Tanoue. Can you give us a high-level overview of pulmonary toxicities related to cancer treatment?

Dr. Tanoue:
So I'm going to actually speak specifically about lung cancer treatment because while 10% of patients with any cancer may experience a pulmonary complication related to treatment, lung cancer patients are at higher risk because they often have underlying lung disease, most commonly COPD, but also interstitial lung disease, occupational exposures that may have cause lung problems, and so forth. And since most patients with lung cancer also smoked, not all, but most, they often have other smoking-related diseases like cardiac disease. And so the likelihood that a patient with lung cancer will have problems with pulmonary toxicity or pulmonary complications is actually even higher than 10%.

So that's the first point. But the second point is that lung cancer treatment is so different than it was twenty years ago and even ten years ago. We have so many more therapies besides chemotherapy, which is still the best treatment for many patients. We have the options of antigenic treatments, molecularly targeted therapies, and immunotherapies. All of those have their own benefits and own toxicities. They're used singly and in combination and that really makes this a prose to pulmonary toxicities more complicated.

Dr. Sylvestri:
With that in mind, what approach do you take when you suspect a patient has treatment-related pulmonary complications?

Dr. Tanoue:
The approach I take with this group of patients isn't really different than my approach to any complex patient. And really is very similar to how we approach patients with pulmonary complications who are in immuno-suppressed from any reason, not just cancer. And I teach my medical students and my fellows to try to approach things methodically, and I think about these as falling into the big buckets of neoplasia, infections, inflammation, and then that dreaded 'other' category that includes things like cardiac decompensation or pulmonary embolism and I think if we keep that simple framework of approaching a patient methodically, we won't miss things and we

have to actually exclude other things to arrive at a diagnosis of treatment-related complications.

Dr. Sylvestri:
Lynn, when you gave your webinar, one of the things that I think was so elegant about one aspect of it was it's getting impossible for pulmonologists to keep up with all the drugs. And some drugs, for example, really might lead to infection, like standard chemotherapy agents, which might lower the white count, whereas other drugs, that's not going to be as much of a problem. I notice that you talked to us a little bit about PneumRX that website where you could plug in the drug that someone's on get some information about toxicity. I'd love for you just to tell me how you use that to evaluate a patient with a suspected pulmonary toxicity.

Dr. Tanoue:
So that website which is an amazing product of Dr. Felipe Calloux in France is an amazing resource because he essentially has collected the literature and so that if you're looking for a single source where you can get your hands on literature, evidence related to other peoples' experience with the drugs you may be dealing with, with an individual patient, that's sitting on that website, it's public access and I have found that such a resource. In particular when I'm looking for somebody else's experience related to a situation that is not common. And all of these new drugs that are coming out, all these new treatments that are rapid-fire being developed approved, released, and used, we don't have a lot of experience with particularly the immunotherapies and the molecularly-targeted therapies. Every time you turn around, there's another one out there and the really challenging thing is when they're used in combination because that clinical experience is very post-release and then we're really depending on each other's knowledge, reporting experience with those treatments. And so I would really encourage people to use that website. It's kept remarkably up-to-date and it really is a resource to the literature.

Dr. Sylvestri:
And can you give us a few more other hints about what you do when you're actually asked to see a patient and where you might suspect pulmonary toxicity? What are some of the first things you do?

Dr. Tanoue:
Absolutely, I think this is the real challenge, how do you approach that patient? And again, I use the same approach as I do for pulmonary complications in an immuno-compromised host, even though not all patients with lung cancer getting treated are immune suppressed. So for instance, the molecularly targeted therapies and immunotherapy don't immuno-suppress the patients, so you have to really keep that in mind. Because their complications are potentially going to be very different than somebody who's on platinum doublet chemotherapy. And so it really, again, should be very methodical, you look at the patient, you talk to them, you look at the timeline of the treatments they've had, you examine them, what does their lung sound like, do they have a rash? And then we have all this data, right, we have laboratory evaluation, we have access to tons of imaging modalities now.

And I think that again if you keep that framework so that we don't get caught in listing a hundred diagnoses, but we think of them in terms of neoplasia, is the cancer recurring, infection, is the patient at risk, inflammation, which includes drug toxicities and then these patients who are at risk for complications like congestive heart failure of pulmonary embolism. I think if you keep thinking along that framework, you won't get caught with the millions of diagnoses and no path forward. Because I think after you do that initial evaluation, the answer of is the bronchoscopy or even a surgical lung biopsy going to help me, and in these situations, bronchoscopy, BAL, and biopsy are really going to help you include infection or the possibility of recurrent or progressive cancer. It will not give you the diagnosis of drug toxicity in most cases; drug toxicity really becomes usually a diagnosis of exclusion and so you have to be reasonably convinced that the patient doesn't have another problem that could readily explain their pulmonary situation before deciding about drug toxicity. And in particular, keeping in mind that if we establish or we land on the diagnosis of this is a complication of treatment, that potentially has huge implications as to whether the treatment can be continued, and in the patient, who's doing well on their therapy, that is a really important decision.

Dr. Sylvestri:
For those just tuning in, you're listening to *Deep Breaths, Updates from CHEST* on ReachMD. I'm Dr. Gerard Sylvestri, and I'm speaking to Dr. Lynn Tanoue about managing pulmonary complications resulting from lung cancer treatment.

Lynn, let's turn our focus to pulmonary toxicity specifically related to lung cancer treatment such as tyrosine kinase inhibitors. What can you tell us about those?

Dr. Tanoue:
TKIs have been used for about twenty years and imatinib, which was the therapy for CML, really changed the landscape for treatment of many cancers including lung cancer. And we know that all TKIs can cause pulmonary toxicity. These are small molecules that act intracellularly to block pathways involving tyrosine kinases. And for lung cancer, the really seminal change in our approach using molecularly targeted therapies was with therapies against EGFR. And dovitinib was the first one developed for that and now probably

used osimertinib or erlotinib most commonly. And unfortunately, as effective as those agents are in the patient with the right targetable mutation, about 8% of those patients develop treatment-limiting toxicities, which includes pulmonary toxicity, predominantly manifesting as interstitial pneumonitis. This does seem to have different prevalence in different populations, so it's more common in Asia; about 4% of East Asian patients who are treated with the EGFR TKI develop interstitial pneumonitis. The prevalence is much lower in a Caucasian population, more like 1 to 2 percent. People who are older males, people who are smoking, etc. are more likely to get pulmonary toxicity, usually interstitial pneumonitis, related to these drugs.

One thing though is the TKIs are not immuno-suppressing, and they do not increase the risk of infection and so, for this population, we don't have to worry so much about that possibility. Recognizing though that pneumonia is the most common infection in patients receiving cancer treatment. When toxicity occurs, it usually occurs reasonably early, within the first few months. But these patients often are maintained on these drugs as long as possible, sometimes years and toxicity has been reported to occur late, as well.

Dr. Sylvestri:
Lynn, what is the time frame, and is that important when you're considering toxicity as opposed to time frame from when the drug is started verus time frame two years later? How does that influence your suspicion of whether the drug is involved in the toxicity or not?

Dr. Tanoue:
Usually, patients who get EGFR TKI pulmonary toxicity do so right around the time that they're showing response. So it's really unfortunate because right as you're seeing their cancer getting smaller and the nodes shrinking, the patient's developing toxicity manifested in the skin as an acneiform rash or start having a different kind of cough, shortness of breath, and different changes on the radiographs that don't look like they're cancer but look like interstitial pneumonitis. And so I think when it's occurring in that time frame, it's actually more likely you're dealing with toxicity.

The longer time frames are always harder because at that point, hopefully, if the patient is maintained on therapy, they're doing well. And so, you're less concerned about the recurrence of the cancer and more concerned about toxicity. But that patient is also living in the world, hopefully reasonably well and so it's entirely possible that they may develop pneumonia, COVID, heart failure, other things that are competing diagnoses in this population that are common. And again, you have to exclude all of those things, particularly when it's a late time course and less likely to be toxicity to be confident enough to then change or stop the therapy.

Dr. Sylvestri:
Now, what can you tell us about pulmonary toxicities related to immunotherapy?

Dr. Tanoue:
The challenging thing with immunotherapy-related pulmonary toxicity is it can look like anything. These are broadly called immune-related adverse events, IRAEs, and we are really seeing them with checkpoint inhibitor therapy, which is really what's available for lung cancer right now. In the clinical trials, about 4% of patients treated with checkpoint inhibitors develop pulmonary toxicity, again, usually manifesting as interstitial lung disease. The post-clinical trial experience generally is that the toxicities are more common because we are using these drugs now in patients who weren't cleared to enter a clinical trial because of the absence of other disease like cardiac disease or auto-immune disease and so forth.

What's described most commonly is a pattern of patchy geographic interstitial abnormality that looks like organizing pneumonia, but every single radiographic abnormality has been described with immunotherapy pulmonary toxicity infiltrates that look like infectious pneumonia diffuse infiltrates that look like hypersensitivity, pneumonitis nodules, and then a phenomenon called 'pseudo progression' where you actually get worsening of the radiograph around areas of cancer. And so I think it has to be on your radar, the possibility of treatment-related toxicity all the time. But you have to really prove that it's not something else before you decide that it is related to the drug.

Dr. Sylvestri:
Lastly, Dr. Tanoue, any final considerations that you'd like to share with our listeners regarding managing pulmonary toxicity stemming from lung cancer treatments?

Dr. Tanoue:
One thing is that we talked about the time frame for targeted therapies and the time frame for pulmonary toxicity related to immunotherapy is actually really interesting because as opposed to other immune toxicities like thyroiditis or colitis, the pulmonary toxicity tends to be later, most of it shows up by several months into therapy, but you can still develop pulmonary toxicity years into therapy. And so, I think this is a situation where, again, it has to be on your radar, you have to be thinking about it; again, always a diagnosis of exclusion but the toxicity risk does not go away if you've been on the drug a long time.

Dr. Sylvestri:

With those final thoughts in mind, I want to thank my guest, Dr. Lynn Tanoue for joining me today to talk about lung cancer and treatment-related pulmonary toxicities. Dr. Tanoue, it was great having you on the program.

Dr. Tanoue:
Gerard, thanks for inviting me. Always a pleasure.

Announcer:
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