

SPEAKER: So when considering intensive therapy upfront, and I talked about thinking about this in patients that have severe disease or cavitary disease, we will use intravenous amikacin if we can in those patients as recommended by the last iteration of the American Thoracic Society guidelines. Now the duration of that treatment is usually two to three months. And realistically, what do we see from that?

So in the studies looking at the experience with IV amikacin, it allows patients to convert their sputum cultures faster, but it has no durable effect at the end of treatment. It doesn't seem to be associated with the ability to attain cure in the long term or the ability to prevent relapse in those patients. And that makes sense because it's an effective drug.

But because it's also a toxic drug, when we use it IV, we have a window of time for which that patient is going to tolerate it. Ultimately, I tell my patients, if we just continue to use this indefinitely, you will start to have hearing loss, or tinnitus, or problems with your balance. Fortunately, we almost never see nephrotoxicity in our patients because we dose the IV amikacin three days a week as opposed to daily. But it's certainly not unheard of. And patients that are at risk for renal insufficiency will have evidence of an elevated creatinine on IV amikacin.

So those are the challenges that we face. We have an active drug. It certainly is effective in patients that have disease. And it helps in patients that have cavitary disease convert their sputum earlier. We also think about it in patients that are headed to the operating room. So because this is such a drug-resistant infection, we employ lobectomies or even pneumonectomies on patients that have disease that's not responding to treatment or that we suspect will be treatment refractory because of the size or the degree of destruction on their CAT scan.

So again, that's how I think about intravenous amikacin. I think about it upfront. I think about it in patients that are about to have surgery. But there's a short window of opportunity there because, ultimately, they will not tolerate it. So we need to think about ways to use amikacin that are tolerated for longer durations of time, that get to the target of the infection via an inhalation route, and, by using the liposomal form of amikacin, ideally go to where the infection exists, and that's within the pulmonary macrophages in the lungs.

So as you probably know, we have been using the old form of inhaled parenteral amikacin for decades. We've used it in our patients because after we complete the IV route of amikacin, that's what we had to choose from. But now we have a drug that's been studied in a randomized controlled trial and has been shown to have activity that allowed for 30% of the patients in that study that received the liposomal amikacin to convert their cultures.

And I'd like to step back and talk about who benefited and who was included in that study. So the patients in that study, that CONVERT study, were patients that had treatment refractory disease. Now, interestingly, the average amount of time that those patients were on treatment before they were enrolled in this study was four years. So these are patients that could not convert their cultures after years of therapy. And they show that 30% of them on the inhaled liposomal amikacin were able to convert their cultures versus about 9% of patients in the guideline-based therapy treatment alone.

Patients often ask me, when are they considered to be treatment refractory? And I think this is an area of a lot of debate. What are the definitions in this disease state? And recently in 2018, there was a consensus statement published, the NTM-NET consensus statement. There was a group of experts around the world that got together to help define what did they agree upon as far as treatment definitions.

And treatment refractory in that statement actually was considered patients who were on treatment and were persistently culture positive after a year of treatment. I actually disagree with that. And I don't know what the new American Thoracic Society guidelines will show. But I think if we treat our patients with three drugs for a year and we wait that long to then consider them refractory, I think that's a disservice to our patients.

So the majority of our patients should culture convert by six months of treatment. And if at six months they're still culture positive, I would consider that patient treatment refractory. And that, in fact, was the definition used in the CONVERT study that patients had to be culture positive for at least six months to be enrolled in this study.