Pulmonary Complications from Lung Cancer Treatment, Part 1:
Chemotherapy-Induced Pneumonitis
by Dr. Gerard Silvestri, Medical University of South Carolina

Dr. West:
Hello, and welcome to our webinar with Dr. Gerard Silvestri on Pulmonary Complications and Lung Cancer. We’ll be focusing specifically on complications of lung cancer treatments. I’m Dr. Jack West, I’m a Seattle-based Medical Oncologist and I’m part of the non-profit GRACE, the Global Resource for Advancing Cancer Education. We’re happy to be partnering with the LUNGevity Foundation to bring you today’s program.

I’m particularly pleased to welcome back Dr. Silvestri, who is a Professor of Medicine in the Division of Pulmonary and Critical Care at the Medical University of South Carolina in Charleston. He did a live a presentation of ours at a program that GRACE ran several years ago in Seattle on the subject of the initial workup and staging of lung cancer, and that became one of our most appreciate podcast partly because of the importance of the topic and partly because Dr. Silvestri presented with such animation and a great connection to the patient audience. So with that, I’m going to turn it over to Dr. Silvestri.

Dr. Silvestri:
Thanks Jack. I’m Gerard Silvestri, I’m a pulmonologist – so pulmonologists are lung specialists. I almost exclusively take care of lung cancer patients. So, to let you know, even though I’m in academic medical center I see between five and seven new lung cancer patients a week, evaluate them, stage them, make a diagnosis and send them off for the appropriate treatment.

Through that process I also take care of patients with lung problems after they’ve been treated for their lung cancer, and that’s what we’re going to be talking about today. I just want to let you know I have no relevant financial disclosure related to this talk. I want to review some of the chemotherapy-induced lung toxicities and also discuss some of the imaging and physiology in the treatment of radiation-induced disease, so called radiation pneumonia or radiation pneumonitis.

One the things I’ll tell you is sometimes it’s really difficult to distinguish between the cancer itself and progression of the cancer, and then, sometimes what the medications and the radiation can be causing. So, it takes an astute patient to say, “Hey, this may be just more than the medicines,” and an astute doctor to say, “Hey, let’s think about some of these other things.”

So for patients I will always tell you that if you’ve been getting treatment for your lung cancer, and the cancer seems to be getting smaller but you’re getting worse in the way of symptoms, you should always ask your doctor, “Hey could any of the symptoms I’m feeling right now be related to the fact that I’m getting these treatments.” So, the diagnosis requires a history of the drug exposure.

You really want to rule out other causes of the changes that you’re seeing on chest x-ray or the findings that patients feel in terms of symptoms; findings on the history, on the physical and imaging. Also, sometimes findings on a biopsy are not always very specific. So it’s the constellation of those findings that make us really think about chemotherapy as a cause for lung toxicity.
So, this slide was sort of built for physicians, but I’ll take you through it. Usually if someone’s going to have a chemotherapy-induced lung toxicity, they have progressive shortness of breath, a low oxygen level, and one of the hallmarks for this is a dry cough and low-grade fevers. Again, some of these are symptomatic of any patient with cancer, but that constellation makes us think more about chemotherapy.

On a physical examination, we generally hear these things called crackles. Folks who remember Velcro, pulling apart Velcro that closes things like slacks or tennis shoes, you open that up, that crackly sound. There are some things on the lung function test, I won’t go through those in detail, but if we do breathing test on a patient we are oftentimes given a clue through this DLCO, the diffusion of oxygen into the lungs that something is amiss.

On the chest imaging we often see patterns, and it’s written here as diffused interstitial or alveolar patterns. But they can be special patterns that we see on the chest x-ray that alert us that it’s not a cancer but something else. We sometimes do blood work, and in that blood work we look for things that suggest that there’s intense immune action going on. So an elevated white blood cell count, which is what fights infection, a segmentation rate and a few other of these findings can tell us on the labs there’s a lot of inflammation going on and maybe it’s not related to the cancer at all.

Then if we proceed to a biopsy – and I’m not suggesting that we always proceed to a biopsy. Sometimes we just withhold the medication, the chemotherapy drug, and see if the problem resolves. But if we do go to a biopsy there’s some classic findings on that biopsy, and those are listed in detail on the right. That’s really doctor speak that you don’t need to worry yourself over. But what you should know is sometimes your doctor will ask for a biopsy to prove that there’s this certain type of inflammation from the chemotherapy.

So there are different categories, it’s not just one size fits all for these injuries. Sometimes the top one called bronchospasm, that’s an asthma-like reaction, some are a pneumonia-like reaction. Some are simply a reaction from infusing the drug in to the veins. Some look like pneumonia, and some look like a heart failure. So you can see a lot of different patterns with the drug-induced lung complication.

What I would tell you, everything I’ve listed on that alphabet soup of a slide doesn’t look like a lung cancer. So if we see these findings on a chest CT or a chest x-ray, it makes us think that it’s not just the cancer but it’s something else. So I think for folks who have been through chemotherapy; there’s many classes of chemotherapies, the most common ones used are the platinum group and the taxane group.

Paclitaxel and docetaxel are main drugs that we use both intravenously to treat patients with lung cancer. It has activity in both small cell lung cancer and non-small cell lung cancer memory. That non-small cell lung cancer includes adenocarcinoma, squamous cell carcinoma or large cell, and poorly differentiated carcinoma. And it’s derived from the bark of the Pacific Yew tree, and it can act against tumors by working within the cell to destroy lung cancer cells; a very good drug, very active against lung cancer.

So the taxanes can cause an acute infusion reaction; that is, it’s almost immediately after the IV is started and the drug is beginning to be infused. You can have this histamine release, so an allergic response, and patients can get a skin rash, shortness of breath, wheezing and a low blood pressure. What that led to is that if we just pre-medicate patients sometimes with steroids, sometimes with Benadryl or sometimes the combination. We can reduce that from about one third of the patients who get this drug to about 2% of patients. Often when you sign up for your
chemotherapy, if that’s what you need, we’ll have the chemotherapy infusion nurse give you these medicines before they give you the drug to prevent the reaction.

So there’s also a taxane-induced hypersensitivity pneumonitis. That’s a fancy way of saying an allergic pneumonia. For all the world, it’s something that looks like a bilateral or both-sided pneumonia. It occurs in the less than 2% of patients and it generally occurs within a few hours up to two weeks after the infusion of the drug. That’s sometimes tough to figure outright two weeks after people get the drug, they might not go to the emergency room and not even remember to tell their doctor that they got chemotherapy two weeks ago.

Sometimes they get misclassified as a regular, old bacterial or community pneumonia. This is definitely a different type of pneumonia and it can get much better with the use of glucocorticoids – it’s a fancy way of saying steroids – that can rapidly fix this process. There have been very rare cases where even after you try that, the pneumonia persists, and very few patients have progressed to a chronic scarring process or even death.

Again, I would alert the audience, the lay audience that when folks see something like this could lead to death, they sometimes get very worried about trying the chemotherapy. What I would alert this audience to think about is the alternative, that we don’t use the best drug, the taxanes are part of the best class of drugs to treat their cancer. So even though there’s a very small risk of a bad outcome, people shouldn’t be dissuaded from using these drugs because by and large they never cause these side effects.

I want to show you a few slides, and I don’t know how well you can see this at home. This is a CT scan of someone’s lungs. Just to orient you, this is the spine in the back, the person is lying on their back; this is the chest in the front. This is the right lung because they’re lying on their back and this is the left lung. When you go through the scanner you’re being sliced like a loaf of bread with those images, and this is just one image through the scanner.

On the left side you can see that these are normal blood vessels, and this dark stuff is just the air going through there. But down here you can see sort of a more fluffy white pattern in the person’s lung, and that is evidence of some hypersensitivity reaction here and here in this lung. The darker parts, the clear parts, they’re normal and not involved with this process.

You can see this is a chest x-ray of someone. This white area up here is an area of hypersensitivity pneumonia that you shouldn’t see. It should be all darker through there.

Again, this is another cut through a CAT scan. You see this is normal, this black area up here, normal air in the lung. But this white area down here and also out here, areas that for all the world can look like a pneumonia, like somebody who comes in with a typical bacterial pneumonia but in fact it’s related to this taxane-induced pneumonitis.

If we were to do a biopsy, and sometimes I often think these things look like fancy artwork, but if we were to do a biopsy in patients with radiation pneumonitis you’d see this area up in the right-hand corner which is this very thickened area. This is the lung of a person and it should have lots more of these open areas. Between this open area where the air comes in there should be very thin walls, and here you can see that there’s thick looking infiltrate in the biopsy specimen.

Again, I want to point out that we oftentimes do not do a biopsy, but if we think that this is what’s going on we would treat the person with some steroids and see if the x-ray gets better. But sometimes it’s hard to differentiate this between the taxane-induced pneumonia and a true
bacterial infection. So sometimes we want to make sure there’s no infection going on and we might take a biopsy and send for cultures in that regard. But by and large we would just hold the drug and see if they better on their own.

So, sometimes – I think many times – for folks who have been through cancer treatment, we combine medicines. For example, I’ll throw out two common combinations, platinum-based combinations. So, cisplatinum and Taxol. So, it’s taxane and a platinum. In one of these combinations is a taxane and gemcitabine – Gemzar is the common trade name for that drug.

However, in one large trial comparing docetaxel – so a taxane – with or without the use of Gemzar, the incidence of interstitial lung disease – the interstitial lung disease is a fancy way of saying scarring lung disease – was much, much higher in the combined therapy group. You can see that’s here, 20% versus 3.1%. So a large increase, a sevenfold increase in toxicity, and they actually stop the trial sooner rather than later because so much lung toxicity occurred. So, these medications probably shouldn’t be used in combination with one another.

There’s also an effect of using a chemotherapy agent with radiation therapy – I’m going to get to radiation later. But the effect of using them together is often called “radiosensitizing”, and sometimes we actually do that on purpose, giving medicine to help improve the way radiation therapy works. So, in this instance of combining some drugs with radiation therapy, pneumonitis or pneumonia and inflammatory pneumonia, is much greater than when you use radiation alone.

There’s something called recall pneumonitis may develop in patients receiving paclitaxel who previously received radiation. So if you had radiation, let’s say six months ago, and then later on they just used the IV chemotherapy you can see somehow the body remembers that you’ve received that radiation and you have this incidence of an inflammatory pneumonia as well. So, we just need to be careful when using chemotherapy agents in conjunction with radiation therapy.

So there’s another, docetaxel, again one of the taxanes, can cause a capillary leak syndrome and usually it causes fluid retention. Capillary leak just means those tiny, little blood vessels that are found throughout the body but particularly in the lungs, they have very, very tight walls to them. But every once in a while those walls loosen up a little bit, fluid can get out and get through them and leak into the lung. So usually it causes peripheral edema, so that means ankle swelling. But sometimes they can cause lung edema – or what’s stated there, pulmonary edema or a pleural effusion – that’s fluid in the linings of the lungs. If you give steroids 24 hours before and 48 hours after, this reduced the incidence and severity if it were to occur.

Gemcitabine, or Gemzar, is overall a very well tolerated drug. But, sometimes when patients get the drug they can report shortness of breath in 10% to nearly a quarter of patients. Usually it’s very mild and they don’t complain much about it, and if you hold the drug or discontinue the drug it most of the time goes away. However, there are some severe cases; the acute respiratory distress syndrome (ARDS) or scarring process interstitial pneumonia, or a lung edema, a fluid process in the lung can also occur. The treatment is to discontinue the drug, to use steroids, and if they have a lot of fluid buildup you can give patients a diuretic.

I do want to mention that there are times when we find ourselves in the quandary of not having another available drug to us. So there are cases where we’ll go back and in a lower dose, challenge the patient again with these medications because it’s the only thing we have left. Again, pre-medicate them with steroids and such in the hope that they won’t have this reaction. So sometimes if pushed up between a rock and a hard place we’ll re-challenge patients with these medicines, and that applies to all the medicines.
Here’s a case, if you look at the top slide, there’s three different slides here. Here’s a case of a patient initially with a diffused pneumonia-like process from Gemcitabine. Here you can see them again, a little bit left, and then later on the lower portion of the lung you see they’re resolving pneumonitis in this patient. So when they first had it, it looked like this, it got a little better and it started to clear and then cleared significantly later on.

Again, this is one of those biopsy specimens. I’m not going to quiz you. It’s okay, I’m not going to tell you what do these biopsy specimens show. But I will tell you that that wall is much too thick and there’s a lot of damage in this wall from leaking fluid into the patient and also causing a diffused scarring process.

Etoposide is another drug we commonly use in small cell lung cancer for those folks who have been through treatment of small cell lung cancer. Again, this can cause what’s called a hypersensitivity syndrome, which is almost like anaphylaxis, like having a terrible bee sting injury. It can also cause acute pneumonitis or pneumonia and also is one that can increase the risk of having radiation damage. With that drug, it would also be withdrawal drug and steroids.