



Lung Cancer Awareness 2018

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- Chagpar Good evening and welcome back to another episode of Yale Cancer Answers. I am Dr. Anees Chagpar, and I am joined tonight by my guest, Dr. Roy Herbst. Dr. Herbst is the Ensign Professor of Medicine in Medical Oncology and Professor of Pharmacology and Chief of Medical Oncology for Yale Cancer Center and Smilow Cancer Hospital. He is with me here tonight to talk about advances in immunotherapy for lung cancer. Thank you so much for joining me.
- Roy Pleasure to be here Anees.
- Chagpar Roy, let us start by setting the stage of what exactly lung cancer is and how bad a disease is it? I mean, are there therapies that are required for this disease or is it something that is already well treated?
- Roy Lung cancer is probably one of the most common cancers diagnosed, it is second only to breast cancer for women and prostate cancer in men, and a large number of people succumb to lung cancer each year. It is probably the top one on the list. So, it tells you how serious it is. The problem is that it is quite common, it is often caused by smoking, but about 10-15% of patients have not smoked and there are other factors that can result in lung cancer, other toxins and other things in the environment. But the real problem is that lung cancer often is diagnosed already in an advanced stage. So, it is no longer treatable with surgery or radiation therapy. In fact, even when it is treated that way, it has a high proclivity to spread. So, lung cancer is a very serious disease, and fortunately, I have a very strong group here at Smilow that studies it and I can tell you over the course of my career, now more than 20 years, the advances that we have seen to treat this disease have been enormous.
- Chagpar Let's take one step back before we dive into treatments and all of the advances that have made in lung cancer, when you talk about lung cancer being diagnosed at a late stage, what we have seen in a number of other cancers is that there has really been a burgeoning of screening, which helps us to find malignancies at earlier and earlier stages where they are most treatable. Are there any advances going on in lung cancer in that regard?
- Roy Yes. Screening is important and quite frankly it has been under-utilized. We have a screening program here at Smilow Cancer Hospital. Right now the data only supports screening people who are current smokers or former smokers having quit fewer than 15 years ago in the ages of 55 to 75 or thereabouts. So, it is a very limited group that gets screened. Even within that group, we are seeing far fewer people coming for screening than could possibly come. In that group, there are a data of large randomized trials that show that those patients, if they get a low-dose CT scan, CAT scan, early lesions can be found, then can be cut out or treated in some way before

they spread. We are doing some of that here. We actually have a large program as part of our lung SPORE. That is a grant that we have in lung cancer; when the patients come for screening, we also use that as a teachable moment to bring the patients in for smoking cessation. We have some very novel smoking cessation programs here that are using some very new messaging techniques along with medication and other counseling. So, that is all very important. I would love to see screening enhanced; of course in order to do that, we need to identify those populations most at risk. Because as opposed to breast cancer screening for example or prostate screening, which many of the people listening might have already had, those are tests where if you find something that is wrong, the biopsy is the next step, so they still require some biopsies. But for lung cancer, imagine if you find something in a lung and you do not know whether it is really a cancer or is it just some abnormality of age and time, going in and taking a biopsy from the lung is much more difficult. So, that is one other reason why I think lung cancer has not taken off as a disease where screening is as common as it could be. But we are really trying to increase that. I actually just came from a meeting where we have a foundation grant from the Bristol Myers Foundation, which is helping us to bring navigators into the community and to all aspect of the community, all the different areas, some of the underserved populations as well to really try to help people to get to our hospital so that they can be screened because if we can prevent lung cancer despite everything we are about to talk about, that is the best way to deal with it.

Chagpar And one of the problems as you said with screening as well is that there are people who have never smoked, who also will get lung cancer and are not eligible for screening.

Roy Absolutely, and I see that all the time, especially since we tend to be a referral center for many of these patients, up to 15% of patients will have not smoked or maybe they have a very light smoking history, you know a few cigarettes in college perhaps, but really not a significant history at all, and we now know that there is a lung cancer that is driven by certain oncogenes, certain proteins that tend to occur more in people who have not smoked, that is known as epidermal growth factor receptor, and we see a good deal of that as well. The therapies for that have truly improved as well, but it is a small fraction of the patients, and even there, we have to worry about the cancer becoming resistant even when we start some of these novel therapies.

Chagpar That is a nice segue way into talking about how we treat lung cancer because it seems to me that lung cancer, like many cancers that we talk about on this show, are really a heterogeneous group of diseases, it is not a one-size fits all, is that right?

Roy I like to tell the students, it is not lung cancer, it is lung cancers because of the heterogeneity. Every patient's tumor is different because it is starting out of a unique

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genetic material. Every person is different and then there are so many different causes whether it be smoking or radon gas or asbestos or some other random event that has occurred, as cells divide. There are so many different variations, and if you think of there being 25,000 genes that make proteins in a tumor, when we do sequencing studies to look at these, we see so many different variations. It is hard to say one size fits all and to have one therapy for all. That is why for some of these what we call targeted therapies, the results have been quite promising, but they are still limited because only a small percentage of patients will have the abnormality that corresponds with the drug that we can give. The majority of patients I would say still more than 80% do not have a specific abnormality, making it even more difficult to figure out how to treat them. So, we have to be personalizing, and that is the mantra of the era – personalized therapy for cancer, and that of course means personalized care and careful attention to the patients complaints and symptoms, that goes without saying and now we have to personalize and look at the tumor, understand what is driving it, what is the gas for that tumor, what are the key parts of that engine that if we knock them out, it would stop working and that is what we are trying to do here at Smilow Hospital.

Chagpar Tell me a little bit more about how you do that? How do you look inside of the tumor and figure out what the gas pedal is and what the brake pedal is and how those mutations are driving that cancer? How does that happen, if a patient presents, they have been coughing up blood or they are short of breath or all of the symptoms that we associate with lung cancer, how do you get to understanding what particular kind of lung cancer that individual patient has?

Roy We are pretty tuned into this now, so if someone does have the symptoms you mentioned, they come in, we find a mass and they get a biopsy. Oftentimes, before I will see the patient, many of the tests that we need to personalize a therapy are already done. So, now, in 2018, what we will typically do is determine what type of cancer it is. Is it small cell or non-small cell lung cancer, those are old terms but still important because small cell is a very different disease. Small cells usually are always associated with a smoking history. Within the non-small cell patients, what we will then do is, we will profile that tumor, meaning we will send off a battery of genes, usually 50-60 to get started to look for different oncogenetic drivers, different abnormalities that will help us to treat in a specific way. One of those is the gene epidermal growth factor receptor where there are several abnormalities that we can then treat with a pill. There is also something called ALK, anaplastic lymphoma kinase, and several others and we will test for those so that by the time we see that patient, we will know whether he or she has that abnormality. We also are now in an era where for many of the others, the other 80% who do not have one of those drivers, we now know immunotherapy can be very helpful. Using the body's own immune system

to attack the cancer, enhancing it with different drugs and therapies that we have, sometimes even in clinical trials, and in order to that, we need to know about something called PDL-1, actually discovered by Dr. Lieping Chen, one of the professors here at Yale a while back, but now we can measure PDL-1 on tumors and we actually have that result before we see the patient in clinic. Then, using all that information along with the severity of the tumor, how many locations it has moved to within the patient, we can design a multi-modality treatment plan. So, what typically happens on Monday mornings at 7:30 a.m., we get together at a tumor board, that is over at the Smilow Cancer Hospital; we have surgeons, radiation oncologists, medical oncologists such as myself, many of our nurse practitioners, nurses, students, fellows and most importantly sitting there for the first 10 minutes is our pathologist, and what he or she will do is they will look at the tumor and tell us the molecular characteristics, you know is it squamous or non-squamous lung cancer, small cell, but then they will review the results of the profiling. So, we will know if we have one of these gene mutations usually before we see the patient. If not, and if someone is being referred and comes in very quickly, we will ask for the tissue so that we can get that done, and we will know – yes this tumor is being driven by the epidermal growth factor receptor, that means they should get an oral drug and now the drugs we have for this are just so advanced, we are in the third generation of drugs. If we find they do not have one of these molecular drivers, we will say okay are they candidate for immunotherapy? If the level of this protein I mentioned PDL-1 is high, some patients might get immunotherapy right off the bat and not even have chemotherapy, that is how strong some of the data are, some of it is immune-derived from work we have done here over the last 10 years. Or if those values are low, we might say, well maybe the patient needs a combination of chemotherapy with immunotherapy or what we really try to do and this is why it is so wonderful working in a place like Yale is we have protocols. We are at a type of place that can raise the bar and actually many of these new therapies are developed and then they are exported out. So, if the patient came in, I would look at all these characteristics, I would work with my team because I really benefit from having such a strong team to advise, and then we might decide well maybe there is a clinical trial where there are 2 immunotherapies being used together because those are shown to have a higher percentage of benefit than one alone, so we are doing it in a clinical study, we are getting drugs from different industry partners. Sometimes, we have drugs that we have developed here at Yale, and that is a specially satisfying that something has been developed in the lab across the street, you do all the toxicity work, it makes it to the clinic usually with the help of a company that is helping to develop. I trained as a fellow in Boston more than 20 years ago and I remember when I went into lung cancer, quite frankly very few people wanted to go into the field. That was the job that was available and I took the job and I focused on it, I learned as much about the biology and treatment as I could and then over the years, I was very involved in the

development of some of the targeted agents and that was during my time at MD Anderson, and now since I have been at Yale, we are really focused on the immune therapy of lung cancer and now the reason I bring that up is the patient that we would have seen 20-25 years ago with advanced metastatic disease, quite frankly that discussion with the patient would have been a very, very hard one because we did not have much to offer and we would offer chemotherapy, which helped a little bit. But now, we have the immune therapy, and the immune therapy is just fantastic. But it is still only working really well in 20% of patients. So, what we are really committed to here at the hospital is figuring out how to help the other 80% and that is with protocols, with molecular studies, bringing the whole team to bear on this disease.

Chagpar Welcome back to Yale Cancer Answers. This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Roy Herbst. We are talking about novel advances in lung cancer treatment, particularly targeted therapy and immunotherapy and some of the clinical trials that are going on in this field. I wanted to pick up on just a couple of things from our previous discussion before the break. One was, you had mentioned that the therapy for people who have epidermal growth factor receptor positive lung cancer is an oral therapy. Does that mean that they do not need chemotherapy and their hair would not fall out and they would not get nauseated, I mean that is really incredible?

Roy It really is. These first studies were done well over 20 years ago with a drug called gefitinib, trade name Iressa, then there was a second drug – erlotinib, Tarceva, and we basically found that in those patients that have these mutations, maybe 1/10 or maybe 2/10 in the United States, much more common in Asia by the way, you could give them this drug and the chance that the tumor would shrink was about 60-70%, so that avoids chemotherapy and now you do have other toxicities; you can get some skin rash, which we help patients manage and some loose stool, but really for the most part, you are taking a pill each day, you go on and you are living with cancer. Cancer is still there but it is under control with these drugs. And now, just in the last year, we have a new drug, osimertinib, trade name, Tigresa, which is a drug that works on even those patients where the first drug stopped working. So, there are about 50% of patients that develop another abnormality and then this drug works. But still, that leaves another 50% for something else and this is where one of the projects in our research group here at Yale lead by Katie Politi and Sarah Goldberg and our colleagues used to look at other agents, both in the lab, in animal models and then in the clinic that can actually help target these resistant patients. But still, no chemotherapy, that is fantastic.

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- Chagpar And so, are you taking a pill pretty much for the rest of your life, mind you it is just a pill?
- Roy Well that would be the hope. You continue to take the pill and it would suppress, kill and suppress the cancer and you would take it for as long as possible. The problem is, it is a Darwinian thing with survival of the fittest and the cancer cells that become resistant will start to grow and they will have a survival advantage. So, I have been doing this now, probably we did some of the first studies if not the first studies when I was in Houston, and over 20 years most patients will at some point need something else, but the good news is, we are trying to stay ahead of the cancer, constantly finding these new drugs, working in partnership with the industry and really this is an effort throughout the world. There is a great deal of this disease in Japan for example, in China they are doing studies. We are doing many studies here at Yale. So, I think that it is very hopeful and certainly if someone has this, you should be quite happy about it and we wish they did not have cancer, but we are happy that we found something that can be treated with a pill and we treat them as long as possible, we move onto the second generation, the third generation drugs when the time comes and we are looking for the fourth and fifth generation right now in a really hard way.
- Chagpar The sad news about that, however, is that the people who have an EGFR mutation are still only a minority. And so, in the majority of patients, we start talking a little bit about advances in immunotherapy, how many patients are eligible for immunotherapy alone versus immunotherapy plus chemotherapy, and tell us more about how exactly immunotherapy works in lung cancer?
- Roy Let's say you have a cancer that is growing. You would think why is the immune system not recognizing this cancer as abnormal and taking care of it, just like it would a virus or a bacterial infection that you might develop? That is because the tumor has gotten smart and it makes a protein that actually blocks the immune system from functioning. So, now what we have is, we have drugs that block that blocker and actually reactivate the immune system. This probably works in almost every patient to a small extent, some more than the others. The problem of course is we cannot give it to the patients that have other immunologic problems because there is a reason why the immune system turns off. If your immune system did not turn off when you are having an infection, you would have inflammation, redness, other toxicities that could be quite harmful. So, if someone already has an autoimmune process; for example, they have severe rheumatoid arthritis or they have immune-related thyroid disease or colitis or anything that is rheumatologic or immunologic, you have to be very careful about using these drugs. The clinical trials have led to a standard of care, where if we do this PDL-1 test on someone who does not have any of these specific mutations but has lung cancer and if that test shows that more than half the cells have this blocker, we will

give them immunotherapy potentially upfront with no chemotherapy and nothing else, and we are doing that. We also know that even in that group and this is the good and the bad and that is why we are coming to work each day, looking for new things, even in that good group, half the patients might not have their tumor shrink, which is a good number so that is why we have to look at new combinations and we are doing that in a very scientific and caring way and that is clinical trials. We have clinical trials right now within our lung group, we call a DART, disease aligned research team, we actually have close to 25 trials running and we look at the patient and we say what is up, what is down, here is a combination that might work better. Then, of course, what if someone gets immunotherapy, what if someone has not come here to New Haven or to one of our care centers but got immunotherapy at someplace else, which many, many physicians have the ability to do this and are doing it very well, but then it stops working. So, there either is no response or patients stop responding and then it starts to grow again, we are developing therapies now in that refractory setting, and the way I hope we will do this best is to biopsy the cancer, so get a piece of it, look at it, dissect it. The clinic has become our lab. Again, the first goal in any clinical practice is caring, attention to the patient, get the symptoms and needs and we do all that, but then really understand from their blood and their tumor what is happening, what is going on with the cancer? And by the way, it is not just in lung cancer, this is really the way we are treating – I know you do breast cancer work and that is I am sure the way the breast group is looking at this right now, triple-negative breast cancer for example is an area where we are seeing these advances. So, it really is pervading all of oncology and the science is driving the way, but as we are understanding the mechanisms of science, people are being helped, people are benefiting and that is what makes it so satisfying given my long history in this field.

Chagpar Tell us a little bit more about immunotherapy. How is it delivered, is it IV, is it oral, what are the side effects? I mean, it sounds like it is this amazing therapy that boosts your immune system and kills off cancer cells, but is it really just that easy?

Roy For some, and it is given intravenously for now. There are some subcutaneous forms being developed. Some day, maybe we will understand enough about it to use it orally, but mostly it is intravenous, it is usually given intravenously once every 2, 3 or 4 weeks depending on the drug, certainly from a patient point of view, I think the less frequent is preferred, though some people find it reassuring to be here a little bit more often. The patients on whom it works extremely well, that 10% or 20%, it is phenomenal. We have patients from 8 years ago who are on the first phase-1 trials, who only received the drug for 2 years and are alive and well, doing great. And then, for many others, they have some benefits, it is more of an intermediate benefit, meaning maybe the tumor might shrink a little bit and then stabilize and that is okay as long as it does not grow. But then, there are some where it might continue to grow or might stop for a

while and then grow again. Those are the ones who we have to then say, okay there are other reasons why the immune therapy is not working completely here – either they do not have the target –this PDL-1 we mentioned, maybe we need to use another target- we are developing this, maybe they have become resistant because other proteins are blocking this effect, let us do a diagnostic and figure out what those are. We have clinical trials for agents that target, what we call the tumor the microenvironment. The cells, not the tumor cells, but the cells that this tumor cells are lying in that might have a role. Because the immune system, again I do not want to get too complicated here, but you need to block what we call the checkpoint, this PDL-1, so you have to release the brakes, but then you also have to have immune cells moving into the tumor. And that does not always happen, some tumors do not get what we call inflamed, they do not get hot – the immune cells do not get there, just like if you were to have poison ivy, your skin turns red. We need to have that happening in the tumor, at the same time, we are unblocking the tumor from the checkpoint. Now, we have to do this in a way that people have minimal side effects or that we manage the side effects. In most patients, the side effects are quite manageable, but imagine if we turn off the rheostat, if we turn off the off knob on the immune system and we let the immune system go on a rampage, you can imagine in certain people it might cause inflammation in the colon, we call that colitis or inflammation in the lung –we call that pneumonitis. If you have inflammation in your lung, that is going to affect your breathing and you are going to come in short of breath. If you have inflammation in your colon, that is going to cause gastrointestinal symptoms. If you have inflammation in your thyroid, your thyroid function might not work so well, meaning you might feel weak and tired; and if you have inflammation on the skin, you might have a rash. So, we have to watch out for all these. The good thing is given that we are one of the first groups to have that here at this hospital and in the system, we are constantly upgrading our ability to treat these abnormalities, we know how to suppress the immune system if we have to, and we even have ways of doing it where it does not affect the efficacy of some of these drugs. So, you can treat the side effects and the patient might still benefit from the anti-tumor effects. In fact, after I leave you here, I am going to a meeting of our Yale Center for Immuno-Oncology Working Group which I am actually the chairman interim, we are searching for a permanent director, but what we are focusing on today are immune toxicities. We are trying to build as one clinical team, the top clinical team we can put together where we have dermatologists, rheumatologists, pulmonologists, endocrinologists, all working together because there are so many doctors a patient might see. If you are a patient, you cannot see every doctor, we have to have a team that can work together, that can say here is a patient with this abnormality – what is causing this and how can we treat it?

Chagpar And immunotherapy, does that work better or worse with chemotherapy? Does it make the chemotherapy work better or does it actually interfere with that a bit?

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Roy Well, you would think it might interfere right. If you are trying to take immune cells and get them to grow, but right now, it looks like it is sort of a push that the immunotherapy and chemotherapy seem to work together in certain disease types and that actually does result in some benefit in patients who may not benefit at all, my personal opinion is at least it is additive, how to make it more synergistic – I bet we can do a little bit better by understanding molecularly how it is working and that would come from clinical work and animal work, and we are doing both here at Yale.

Chagpar Roy, it has been so great having you here as my guest on Yale Cancer Answers. What an amazing advance in immunotherapy in lung cancer show that we have had today talking about clinical trials and how this is really moving the needle. Until next week, this is Dr. Anees Chagpar wishing everyone a happy and healthy week.