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Spotlight on the Rare & Challenging EGFR Exon 20 Insertion in NSCLC

Announcer:
This medical industry feature titled "Spotlight on the Rare and Challenging EGFR Exon 20 Insertion in Non-Small Cell Lung Cancer," is sponsored by Takeda.

Dr Heymach:
My name is Dr John Heymach. I'm a Professor of Medicine and the Chair of the Department of Thoracic/Head and Neck Medical Oncology at the University of Texas MD Anderson Cancer Center.

Today we're joined by Dr Michelle Shiller. Dr Shiller is an expert pathologist and the Associate Medical Director of Genomics and Molecular Pathology Services at Pathgroup. She is also the Medical Director of the Division of Cancer Genetics at the Baylor Sammons Cancer Center.

Dr Shiller, welcome to “Spotlight on the Rare and Challenging EGFR Exon 20 Insertion in Non-Small Cell Lung Cancer” podcast.

Dr Shiller:
Thank you, Dr Heymach, I’m happy to be here.

Current epidemiology data shows that lung cancer is by far the leading cause of cancer-related deaths worldwide, with approximately 1.8 million deaths in 2020.

Dr Heymach, can you help us understand why patients with lung cancer experience such poor outcomes?

Dr Heymach:
Yeah, well I think the primary reason is that in lung cancer patients survival is heavily based on the stage at diagnosis. And, unfortunately, for lung cancer, the majority, about 60%, are already metastatic at the time of diagnosis.

Survival for patients with metastatic disease are unfortunately nowhere near where we'd like them to be. Currently, about 6% of these patients were metastatic when they're diagnosed are expected to be alive at 5 years.

Dr Shiller:
You know, we know there are different types of lung cancer. What are the broad categories of lung cancer, and how are they defined?

Dr Heymach:
Yeah. Well, you can divide lung cancer broadly speaking into two major groups, small cell, which is the most aggressive type, and non-small cell.

Non-small is the most common of those; it's about 85%.

And you can divide non-small cell up into three major groups: adenocarcinoma, which is about 50%-60%, squamous which is about 20%-30%, and then a third group that has a mixture of other subtypes.

Can you explain what a driver mutation is and how that impacts how we choose a therapy?

Dr Shiller:
Driver mutations cause dysregulation of signaling pathways which will lead to the accumulation of tumor cells due to increased cell proliferation and survival. And because those key roles driver mutations play in the progression of cancer, it's critical to try to identify whether a patient has a mutation in one of these genes that is driving the cancer's growth in order to identify therapies which can target

those alterations and have a more specific effect on the cancer itself.

Adenocarcinomas and squamous cell carcinomas are both driven by numerous oncogenic mutations.

And in patients with adenocarcinoma, the most common are KRAS mutations, occurring at around 30%. And then EGFR mutations are the second most prevalent; they average to approximately 15% of patients.

Dr. Heymach, what are some of the elements of the EGF receptor structure and physiology that underlie its function?

Dr Heymach:
EGF receptors are what we call transmembrane proteins. That means they go across the membrane. There's a part outside the membrane, the extracellular domain, and that binds the ligand. And ligand in this case is EGFR. And the intracellular domain has the business end, if you will, the part that's active is called the tyrosine kinase domain.

And what the tyrosine kinase domain does is it has a little binding pocket. Around that binding pocket is something called the C-helix. That kinase activity is what turns on all the intracellular signaling inside the cell that gets the cell to proliferate or divide or survive or to grow new blood vessels; all the things that signal into a cell that can turn it cancerous if it's uncontrolled.

Dr Shiller:
Can you help me understand a little bit more the normal function of the EGF receptor?

Dr Heymach:
Yeah. Well, normally, as I mentioned, a ligand binds and it turns on the receptor. The way it does that is that the receptor actually homodimerizes, meaning the two receptors come together when the ligand binds. And when it homodimerizes, or it can also heterodimerize, the EGF receptor can interact with other receptors as well. It causes the receptor to change its shape, and then we get these other proteins to bind to the intracellular domain.

When it's activated, then it turns on some signaling pathways downstream. One pathway we think of is called the RAS/RAF/MEK pathway. Another pathway we think of is the PI3 kinase/AKT/mTOR pathway. This receptor turns on cells and tells it to divide, it tells the cells to survive. It often tells the cells to metastasize and to grow more blood vessels and do all sorts of things that can help a tumor grow.

Dr Shiller:
Well, you know, then let's get a little bit more into that. So you mentioned the C-helix. Can you expand a little bit more about the role of the C-helix in the normal function of the EGF receptor?

Dr Heymach:
Yeah. So when the EGF receptor is activated, the kinase domain itself undergoes some changes and it's a little tough to visualize, but if you've got sort of a pocket that this ATP fits into, well it's got a protein structure around that pocket. And part of that pocket where the ATP binds is a structure called the alpha C-helix.

The C-helix is a piece of a protein that's just shaped like a helix. It just, you know, when the helix is pointed outwards, the kinase is inactive. When it gets pushed inwards in the right confirmation, it turns on. So the helix and the loop, these are key parts of the structure.

Dr Shiller, can you explain what happens when these receptors get mutated, and it happens in lung cancer. What's the consequence from a tumor perspective?

Dr Shiller:
You mentioned already receptor ligand binding leads to receptor dimerization and phosphorylation, and biologically phosphorylation activates something right? Now that activation may be a silencing or it may be an upregulation but, nonetheless, the active phosphorylation turns something, a function on, or activates it. And then that has effects downstream in pathways involving key cellular processes.

Mutations in EGFR result in increased or sustained phosphorylation of the receptor without requiring stimulation of the ligand or binding, so they are – one word we like to use is constitutively activated or turned on without being able to turn off, as you say. And, ultimately, resulting in tumor development and immortalization of that population.

Dr Heymach:
Do you want to talk about key areas where these mutations, in particular, occur in EGFR-mutated lung cancer?

Dr Shiller:

EGFR itself has 28 exons. However, when we're talking about lung cancer, and in EGFR they're typically clustered within the first 4 exons of the domain called the tyrosine kinase domain, which is a functionally active domain; and in EGFR, those exons are 18 through 21.

Now deletions and insertions in exon 19 and point mutations in exon 21 are the most common alterations accounting for, when you look at all EGFR mutations as a broad category, 85% of EGFR mutations.

So the others are primarily point mutations occurring in exon 18 and insertions in exon 20.

And although less common, EGFR mutations at exon 20 have important impacts, as I said, on therapeutic decision making.

Dr Heymach:
So you mentioned that exon 20 is about 10% of the EGFR mutations, so something like 2% of all non-small cell lung cancer cases as a whole.

And while that sounds like a small percentage, of course that's as common as some other subgroups.

To better understand the effect of these mutations, can you describe some of the consequences of these exon 20 insertions?

Dr Shiller:
Absolutely! And this goes in a little bit to what you described previously, but these exon 20 insertions generally occur within the loop following the C-helix that you so beautifully described for us. The insertion pushes the C-helix out of the binding pocket from the C-terminal side into its inward or active confirmation. This allows it to interact with the phosphate binding loop of the active site that's situated between the N- and C- lobes. And the ultimate result of this is constitutive activation of EGF receptor signaling.

Dr Heymach:
So from your perspective, what's the consequences of those changes in the protein structure?

Dr Shiller:
It gets locked into the ATP pocket and results in steric hindrance. So, essentially, the size of the binding pocket is reduced, and this prohibits efficient binding of the EGF receptor tyrosine kinase inhibitors.

So for patients receiving EGFR tyrosine kinase inhibitors, how much worse are the outcomes in patients with exon 20 insertion mutations than patients with the more common EGFR mutations?

Dr Heymach:
Yeah. Well, if you start with the EGFR inhibitors that we've had available to us, you know, for the last 10-15 years, you know, we called these first-, second- or third-generation inhibitors.

You know, if you take all the patients with classical mutations, outcomes for treatment with first-, second- and third-generation drugs are between 11 and 19 months or so in terms of progression-free survival, how long it takes the tumor to start growing.

By contrast, if you take the same drugs and look at exon 20 insertions, it's typically 1.5 to 3 months or so before they start growing.

Dr Shiller:
Well, with the recent approvals of mobocertinib and amivantamab, use of these products may change your treatment approach, but we'll get to that later.

Dr Heymach:
Yep.

Dr Shiller:
Wonderful. Well, can you help us understand even more so what you're seeing in your own clinical practice with respect to these unique EGFR mutations and so on as you incorporate that into your patients on a daily basis?

Dr. Heymach:
Yeah. Well, happily this is something that’s really changing pretty dramatically. Up until recently, people with these unusual or atypical EGFR mutations had much worse outcomes than patients with a classical EGFR mutation.

You know, there's one retrospective study from a few years ago where the median survival for people with an exon 20 insertion was about 16 months. Those with classical mutations was about 33 months.

Dr Shiller:

Yeah, you know, Dr Heymach, this is very clear that these patients don't respond well to most currently available therapies. So how does this affect their quality of life?

Dr. Heymach:
Yeah. Well patients have a lot of disease-related symptoms that it really does adversely impact their quality of life.

First of all, virtually all patients, or more than 90%, actually have fatigue. About 70% of patients have some pain and/or shortness of breath. Cough often goes along with it. Sometimes it's a dry cough, what we call a nonproductive cough, other times they're coughing up phlegm. And, occasionally, they're coughing up blood as well, what we call hemoptysis.

And, you know, for at least half of the patients, these disease-related side effects actually impact their ability to just do their normal activities of daily living, what we call their ADLs in terms of household chores, going to the store, social activities.

Patients can also experience headaches and visual changes and sometimes that's secondary to brain metastases which is a common problem with people with lung cancer. And brain metastases can cause all sorts of other side effects that can affect their balance, their ability to walk and get along, you know. It can have a wide variety of side effects, but headaches and visual changes would be two of the common ones that have from that.

And so, if you look as a whole, these symptoms really do affect patients' quality of life.

Dr Shiller:
So, you know, we've already heard that there are 2 therapies available for the patients who have the EGFR exon 20 mutation. Can you give us more information about those therapies?

Dr. Heymach:
We now have two drugs that are FDA approved.

The first one is amivantamab. Amivantamab is a bispecific antibody. And so this bivalent antibody, one part of it binds the EGF receptor, the other part of it binds something called c-Met. So this is now approved for people with advanced or metastatic non-small cell lung cancer with EGFR exon 20 insertions as detected by an FDA-approved test if their cancer has progressed after receiving a platinum-based chemotherapy.

More like the typical tyrosine kinase inhibitors that we've been using for a number of years, but it's really designed to be specific for exon 20 insertions; this one's called mobocertinib. So this is an EGFR inhibitor that's given daily orally and, as we talked about before, EGFR exon 20 presents certain challenges for a drug to inhibit, and this one's specifically designed to sort of fit into that reduced tyrosine kinase pocket that makes it hard for standard drugs to bind in there.

And mobocertinib is approved for use of adults with EGFR mutant non-small cell lung cancer if the EGFR mutations are in that exon 20 region again, if their insertions in EGFR exon 20. And if that was diagnosed with an FDA-approved test. And, again, this is for patients whose disease has already progressed after platinum-based chemotherapy.

Well, Dr Shiller, it's been great discussing this with you, so thanks so much for your insights and your great discussion of driver mutations and the pathologic aspects here and for non-small cell lung cancer. It's really been a pleasure chatting with you.

Thank you to our listeners as well.

And, also, please stay tuned for our upcoming podcast where we'll focus on the efficacy and safety of mobocertinib and its recent approval for the treatment of patients with EGFR exon 20 insertion positive non-small cell lung cancer whose disease has progressed on or after platinum-based chemotherapy.

Announcer:
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