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A Case Review: Treatment-Naïve Patient with Advanced NSCLC

ANNOUNCER OPEN:
Welcome to Project Oncology on ReachMD. This segment, entitled A Case Review: A Treatment-Naïve Patient with Advanced NSCLC is provided by Prova Education.

Joining us today at the University of Chicago Medicine is Dr. Everett Vokes. Dr. Vokes is Physician-in-Chief, University of Chicago Medicine and Biological Sciences as well as the Department Chair. Joining Dr. Vokes is Dr. Tanguy Seiwert. Dr. Seiwert is Assistant Professor also at the University of Chicago, as well as the Associate Program Director for its Head and Neck Cancer Program.

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Dr. Vokes:

Hello, I'm Everett Vokes. I'm Chairman of the Department of Medicine here at the University of Chicago. Welcome.

Dr. Seiwert:

Hi, I'm Tanguy Seiwert. I am an Assistant Professor also at the University of Chicago, and I'm the Associate Program Director for the Head and Neck Cancer Program here at the University.

We have a number of cases today and we'll start out with a case of lung cancer. Dr. Vokes, I wanted to present to you a 55-year-old man with no smoking history who presents with a cough and hemoptysis. On further workup, he is diagnosed with an advanced non-small cell lung cancer, Stage IV, and this turns out to be an adenocarcinoma on pathologic review. Molecular testing is done and it turns out that this is positive for one of the classic EGFR mutations, it's a deletion 19 mutation, or deletion 19, exon 19 deletion. How would you approach this patient?

Dr. Vokes:

Yes. Thank you very much. This sounds very much like a classic mutation-driven lung cancer and typically those are seen in middle-aged older, sometimes younger patients, who are nonsmokers, as this patient was, and they are then mutation tested and in this case a deletion 19 is found which is one of the common and very, very sensitive mutations to an intervention with one of our tyrosine kinase inhibitors and we have an option here to do that as first line and that would be the standard of care. And the available agents are, there's gefitinib back on the market, that's the oldest available drug, but then it became rapidly unavailable, and it just recently came back. Erlotinib is probably the drug that would be used by most and has been traditionally in this space for, I think, kind of a decade now, and then more recently is afatinib, a so-called second generation tyrosine kinase inhibitor that may be a little bit more toxic but is also highly active. I think all three are an option. Intriguingly, all of the data that come from randomized trials in this population, comparing these drugs against chemotherapy, showed an increase in progression-free survival, but survival then was never different, and the reason for that is likely the fact that patients who get chemotherapy first then second-line would get one of these agents. There

is a hint, though, from retrospective analysis of two trials looking at afatinib, that survival actually is better, and that is specific to deletion-19 patients and so you could make a case that afatinib might be a preferential agent for this population, although that is not universally accepted, and it's certainly still very much acceptable to use erlotinib or gefitinib.

Dr. Seiwert:

Yes, now thank you for that and it seems like also there's obviously a lack of comparative trials between these EGFR agents, and that makes it harder to compare them. So, clearly, the choice should be an EGFR agent, an EGFR TKI, as a first-line treatment option.

There's a lot of talk now in lung cancer about immunotherapeutic agents and this is maybe a bit premature, but would you ever consider an immunotherapy in the first-line treatment of a patient just like this?

Dr. Vokes:

So, the question is very interesting, Tanguy. The lineage of how do we label something comes from the chemotherapy era and I think when we talk about first-line, second-line, we probably want to limit that to chemotherapy, because for somebody with a mutation, I think the intervention should be a tyrosine kinase inhibitor and likely, for at least half, those with the T790M mutation, the second-line treatment should still be an EGFR inhibitor. That, of course, is emerging. I think the first-line after somebody truly fails a tyrosine kinase inhibitor and has no longer that option, for me would be chemo. Immune therapies, though, are really, really intriguing and approved as second-line, meaning after chemo, but for the patients with a mutation it's a little bit less well known. There is suggestion that those patients respond somewhat less. They do response, but less frequently than patients who have a smoking-induced lung cancer, that the number of neoantigens is less, that somehow the immunogenicity of the tumor is less, and response rates do track a little bit lower. So, I wouldn't say that an immune therapeutic drug should never be used in a patient with an EGFR-driven tumor, but it wouldn't be an early choice.

Dr. Seiwert:

Yes. No, I think that's very prudent and based on the data, really it's in the second-line setting that immunotherapy should work and even there, based on the large Phase III studies with nivolumab, it seemed like, at least in a subgroup analysis, that there was the least activity in these EGFR-mutant patients. So, I think we definitely need more data and it's interesting to follow, but essentially you would keep the paradigm of using an EGFR inhibitor intact and I think that's what most people believe.

So, okay, this patient is treated with let's say afatinib, and after 3 months though he shows an increase in the tumor size and on CAT scans there are new, additional, supraclavicular lymph nodes that are suggestive of progression. The patient is biopsied and additional molecular testing is sent off and in this case the patient has the exit mutation, the resistance mutation of T790M. How would you approach this patient in this case?

Dr. Vokes:

So, the interesting part here is that you do need to do a second biopsy and that was clearly done. So generating that knowledge as to why is a patient progressing, is an important feature of how we manage these patients at this point. About 50% of the patients then have a second targetable lesion, that's the T790M mutation. There are other resistance mutations as you know, or resistance patterns, as you know, that can come up such as small cell lung cancer conversion; a met can emerge. There are other mechanisms that we can't target quite as elegantly. But, we certainly know what to do for T790M mutations, in fact, there is a drug called osimertinib. The brand name is Tagrisso. It was formerly known as AZD9291. That is a so-called third generation EGFR inhibitor and that is now approved and would be the choice for this kind of a patient.

Dr. Seiwert:

So, the patient gets treated with osimertinib and has actually a good response. Has again actually achieved a partial response and has disease control for about 10 months. At that point, though, the patient becomes again symptomatic, has recurrent hemoptysis, and CT scanning him shows that the lesions are regrowing. Now we've exhausted two lines of EGFR inhibitor. What would you do in this situation?

Dr. Vokes:

Well, now I think it's time for chemotherapy, and the patient has adenocarcinoma, was not bleeding, so the standard of care would be a doublet with chemotherapy that would be cis or carboplatin with pemetrexed. You could argue to also treat the patient with carboplatin and Taxol and bevacizumab, and that would be certainly another option. What's frequently done in practice is that patients get carbo or cisplatin with pemetrexed and bevacizumab. I think that that is much less well-supported in clinical trials. So, to me, it's either a doublet, that's with pemetrexed, or the triplet that would be Taxol based.

Dr. Seiwert:

Very good. So, essentially we're going back to the chemotherapy paradigm. How would then the second- and third-line treatment, counting chemotherapy now as the lineage of treatment look if this patient progresses eventually, and everybody will obviously progress?

Dr. Vokes:

Yes. It's very interesting because you already now have given three treatments in the old counting system. In the new counting system I would say the patient got TKIs for EGFR and now first-line chemo, so what do we do now after failing that? The traditional approach would be docetaxel and that certainly is an option, although in a recent randomized comparison between docetaxel and nivolumab, nivolumab won, not on progression-free survival where there was rapid falloff on both arms really, but then in long-term survival, overall survival, nivolumab looked better. The only caveat here would be, as we previously mentioned, that this patient is a nonsmoker, has mutation-driven tumor, and therefore it might be that the response rate would be on the lower side for this kind of patient. Now an area where you've actually been interested in would be testing for PD-L1 on the tumor, and I might actually ask you to comment on that, since that's something that you've been very interested in.

Dr. Seiwert:

Yes, I think with EGFR mutations we have an excellent biomarker and we understand that field quite well. For immunotherapy we would love to have a biomarker that's as reliable, as accurate. Right now the best data we have is with testing for PD-L1 expression by immunohistochemistry and it's not quite as good as genetic testing. It seems like PD-L1 immunohistochemistry is able to enrich a population that is more likely to benefit from immunotherapy, but regardless of which study and even which tumor type to look at, there always is, in every study of PD-L1 immunohistochemistry, there's about 10% of patients that are PD-L1 negative that still have benefit and some patients have really remarkable benefit. So, I personally think it's a good marker to potentially get a sense if you're more likely to benefit, but it is not a marker in my mind, and there's some debate that's ongoing, to exclude a patient from treatment. So if, in a setting like this patient, where you feel like maybe the EGFR-driven tumor may be less likely to benefit, it might be a good idea to do the PD-L1 testing to at least provide some guidance. And one drug right now is actually approved with a companion diagnostic of a PD-L1 immunohistochemistry. That would be pembrolizumab. So, I think it's reasonable, but really the role of PD-L1 testing is still being debated and figured out. I think there are newer biomarkers that are emerging and though they're really early in development, but the hope is that one of these newer biomarkers in the future will provide us a more reliable prediction of which patients we should and shouldn't treat.

Dr. Vokes:

Yes. So, in reality, in the end, this patient is likely going to get both, but what the PD-L1 testing might facilitate is a decision as to what should come first. Would it be pembro and nivo or docetaxel?

Dr. Seiwert:

So, let's do a little bit of switch here. Let's assume for a moment that this patient was not EGFR mutant, but had instead an ALK translocation of one of the potentially other targetable genetic aberrations. How would you approach this patient now? How would the case scenario be different?

Dr. Vokes:

That's really very interesting because clinically you could totally do that. There's huge overlap in the clinical characteristics between EGFR-mutation-driven tumors and ALK-driven tumors. Both are more common in females and in nonsmokers. So, the clinical presentation would likely be very similar. The choice of drugs would be different with crizotinib being the agent of choice for first-line, having been shown to be superior to chemotherapy there, and likely would last for several months, and at some point again progression would occur as it always does when patients are treated with tyrosine kinase inhibitors. And Bob Dougle and others have done work to describe those resistance mutations. They're less necessarily targetable and we don't have a clear line of working against those. What we do have, however, are second generation, or maybe they're third generation, ALK-targeting drugs and they have been tested second-line. They may also be very active first-line. So, ceritinib is the one that is approved and on the market and that is the one that would come second-line after crizotinib. There's a drug, alectinib which is also highly active but, to my knowledge, not yet approved, and that would in the future likely be another choice. It is also possible, as you mentioned, that the patient could have a RAF mutation; that is targetable with dabrafenib and there's again investigations going on combining that with trametinib, a MEK inhibitor. Those are smaller studies. They're much less definitive. They just tell us that when a patient has a targetable mutation, it may make sense to give a tyrosine kinase inhibitor that would act against that specific mutation. RET is another one that can be seen and comes to mind, but

may be a little bit harder to target in clinical practice.

Dr. Seiwert:

Yes, I think it's really remarkable that all of these mutation-driven lung adenocarcinomas actually have a lot of similarities, as you pointed out, and maybe Trk is the other one that fits into this category and seems like we now have a whole spectrum of those. You know, with **(inaudible)*15:06** the interesting part is obviously also is a failure pattern with CNS recurrences is interesting and alectinib seems to have, and some of the other newer generation agents are really active here. So, I think it's very exciting and interesting to see these second/third generations become available. In EGFR we already have one. In ALK we have ceritinib. So, I think it will be very interesting to see how this field emerges, and it's still a very exciting time, I think, for lung adenocarcinomas.

Dr. Vokes:

Yes. I agree. Much progress to be made still, but much progress has also been made.

Dr. Seiwert:

Good. I think with this we can conclude this case. Thank you, Dr. Vokes.

Dr. Vokes:

Thank you.

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