2020 Target Therapy Forum

EGFR Session

Current & Emerging Treatment Options Upon Acquired Resistance to Osimertinib- Part 1

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Dr. Jared Weiss: I have the great privilege of introducing my colleague, whose data I've already shown Dr. Zofia Piotrowska from Harvard Medical School.

Dr. Zofia Piotrowska: Thanks so much, Jared. Can you hear me? Okay,

Dr. Jared Weiss: I can hear you just great. And your slides look great.

Dr. Zofia Piotrowska: Awesome. All right. Thank you everyone. It's such a pleasure to be here. Thanks to Jack and Jared and all of GRACE for inviting me to be a part of this event. It is a beautiful day here in Boston, and I'm very sorry that you all can't join us in person and the sun is shining. The weather is not too hot, not too cold, so it's a beautiful day, but I'm so glad that we're able to do this virtually and to have this exciting session. So I will be covering today the topic of acquired resistance to Osimertinib, a drug, which I will also say many patients know by its brand name Tagrisso. So just to know that we use those names interchangeably, I think that this is becoming a bigger and bigger problem and challenge that we are facing in the clinic and something that many are working to overcome and develop better and more effective treatment strategies. So that's going to be the focus of my talk over the next 20 minutes or so.

These are my disclosures like Jared, you know, I have worked with many companies that are involved in this space, although none of my work has kind of directly been related to what I'm talking about here. And I also receive research support for clinical trials that

we're running at MGH. So as Jared, very nicely summarized and highlighted, osimertinib is really, I think for all of us the preferred agent for patients who are newly diagnosed with EGFR mutant lung cancers. And that is really based on the FLAURA trial, where we saw a nice improvement in both progression-free and importantly, overall survival over the older drugs, which we often refer to as a category as first-generation EGFR inhibitors drugs, like erlotinib and gefitinib. You know, I think that the treatment with osimertinib has been so successful for kind of a few key points. The one big one that we talk about a lot is, osimertinib is a drug that has very good penetration into the brain and central nervous system.

And this of course is a very important advantage in a disease where CNS metastases are quite common and controlling. Those metastases can really have an important impact, not only on how long patients are able to live with cancer, but as again, Jared alluded to on their quality of life. So I think one of an important aspect of also osimertinib is it's good brain penetration. It's also a drug that was developed to be relatively sparing of wild-type EGFR. And wild-type GFR is something that's present in many parts of our body, not just the lung and particularly in the skin and in the gut and the inhibition of wild-type EGFR by these drugs that are called EGFR inhibitors. I think it really leads to a lot of the side effects that we're used to seeing, particularly with the older drugs, things like diarrhea, GI side effects, rash. And as we've become smarter and develop newer next generation drugs like osimertinib, we've been able to develop drugs that are smarter and more specific to the abnormal mutant EGFR in lung cancer cells and have less effect on that normal ETFR.

And as a result of that, we've seen better side effect profiles with these drugs. As we saw again, nicely highlighted by Jared, and so many patients not only live longer, do better on these drugs. We also see that they have a much better quality of life and feel better. So, I think as a result of all of these, you know, osimertinib, and again, in countries where it is available, it is a preferred first-line agent for EGFR mutant lung cancer. There are many exciting combinations that are being developed. And I think it's important to say that we can't rest here. It's not that we've reached the panacea. There's still much work to be done, and we're going to continue to try to develop even better drugs or combinations to improve upon the standard of care. But today in 2020, I think osimertinib is our standard of care. And as a result, you know, acquired resistance to osimertinib and particularly to osimertinib used as an initial therapy for EGFR mutant cancer is becoming really the major clinical challenge that we are seeing in our clinic. So that's what we're going to focus on today.

What, how do we approach patients who are starting to develop progression on osimertinib and how do we select next line treatments for them? So I've kind of put

together this framework for how I think about progression and acquired resistance as a first step. You know, when patients have disease progression that can be suspected either based on imaging that shows it or based on symptoms. I think it is important to

get kind of a full picture of what's going on with the cancer, get restaging scans, not only of the chest abdomen and pelvis, but also from any patients to repeat a brain MRI, to see, is there any brain progression as well? And I think here it's important to distinguish between something that we often refer to as oligo progression where oligo really means a single or limited sites of disease. And so that means someone who might have progression, for example, in a single site, a lung nodule that's growing while everything else is controlled, or a brain met that has come up, but everything else is a stable and not growing. For those patients, we often will consider what we term kind of broadly as local therapy.

So here we're referring to commonly radiation as an option. Although in some cases we also consider other strategies like surgery radio-frequency or cryo ablation, which are procedures done by interventional radiologists to really address that single site of disease based on the idea that other sites of disease likely are still being controlled by osimertinib. I think often in parallel was doing local therapy or in patients who have more multifocal progression, where you have multiple sites of disease that are growing. It really important to try to assess for resistance mechanisms, to have some written up in selecting what our second line therapy will be. So I think the first thing in talking about this particular subject is to talk about how do we assess for resistance mechanisms. And I believe that there may be other sessions in that during this seminar today, talking about tissue versus liquid biopsies, but I thought it was worth spending a moment kind of talking about how we think about tissue and liquid biopsies for patients who have progressed on osimertinib.

I think for a long-time tissue biopsy, where we're actually going in with a needle and sampling a site of growing disease has been our gold standard for evaluating resistance mechanisms to these drugs. Tissue biopsies, you know, have many key advantages. They're really what we use to identify all known resistance mechanisms, including something that we call histologic transformations, which I'll touch on in more detail in a moment. But really what we're talking about here is a change in the basic kind of histology of the cancer for, from what is most commonly a non-small cell lung cancer and something we can term adenocarcinoma, which describes what a pathologist sees under the microscope when they look at the cancer, into a slightly different type of cancer called a small cell carcinoma, which is something we've seen for, even with older generations of drugs. And also, recently we've seen some cancers that transformed from an adenocarcinoma to a squamous cell carcinoma.

That right now is something we can really only detect by tissue biopsy and not on liquid biopsy. In general, tissue biopsies are also have higher sensitivity than plasma, when we do have enough tissue in that biopsy to be able to do the molecular testing that we need to do. However, tissue biopsies can sometimes be limited by the fact that often

we're getting small pieces of tissue of a needle biopsy, where a radiologist or a pulmonologist is only able to take a small sample. And sometimes we get back a result that's called quality not sufficient QNS, or where there's not sufficient cancer cells to be able to do the testing. I think of course, from a patient perspective, rather the biggest drawback of a tissue biopsy is that it requires an invasive procedure. It requires a trip to the hospital. Often at least a day surgery stay sometimes even an overnight stay and it has some risk associated with it. And that is can't be underestimated when we think about doing these procedures.

Furthermore, not all patients are candidates for a tissue biopsy sometimes based on the location of the tumor, it might be in an area where it's not easily accessible or in a bone where it's harder to get enough to sample for actually good molecular testing. And because of co-morbidities other, other medical conditions that the patient may have that increase the risk of tissue biopsy, it may not always be appropriate. So in the last few years, we've also developed this technology that we often call a liquid biopsy or analysis of circulating tumor DNA. DNA that's actually shed into the circulation by cancer cells. The biggest advantage of a liquid biopsy is that these are, these are easy non-invasive blood tests. I think one of my colleagues always uses the kind of example, and says, not everyone has access easy access to our radiologist or pulmonologist, but everyone can find a good phlebotomist, which are the people that do blood draws, and you can do this in the clinic or at home.

And it's very easy to get. And that is, I think the biggest advantage of liquid biopsy is it often has a quick turnaround time. You send up a blood test, you get back a result within a week or so. And liquid biopsies indeed can identify many key resistance mechanisms that we see. In particular, some of the resistance mutations like T790M, which Jared briefly mentioned, and some of the other EGFR mutations that we see however, the main limitation, I think right now of liquid biopsy is that it does not identify histologic transformations, that small cell transformation that we talk about. And we've also seen that it may not be as reliable in detecting some other kinds of genetic events, which are fusions or gene amplifications as a tissue based test. Also, I think important to recognize is that some cancers do not shed enough circulating tumor DNA, enough DNA into the circulation to be detected and therefore limiting the sensitivity of liquid biopsies. In those cases, you know, we sometimes call those cancers, non shedding cancers.

And I think there, it's important to say that if you get back a negative result from a liquid biopsy, it should, once you consider a tissue biopsy still, if it's feasible, because I think that liquid biopsy doesn't necessarily mean that there is no resistance mechanism to be found, but just that we haven't identified enough cancer DNA there to see it. So how do I think about using these two in the clinic? I think largely because of this issue of

histologic transformations, which is something that we have to look for in patients who progress on osimertinib and in particular for patients where we might see kind of more rapid cancer growth, or new many new sites of disease, where we might worry about a small cell transformation having occurred. In those situations, I kind of tip the balance towards a tissue biopsy, and I think it's important and worthwhile to get that, even though it does require a procedure. And I recognize that that is something that we don't take lightly for our patients. However, I think liquid biopsy is a great tool and there are many situations in which a tissue biopsy can't be obtained in those cases, I think a liquid biopsy is important. And again, I think the key point here is that if possible it is important to get an assessment of resistance mechanisms because they can help inform subsequent treatment.