2020 Target Therapy Forum

The Gap Between the Need for and The Execution of Molecular Testing

Role of Liquid Biopsies vs. Tissue Biopsies

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Dr. Jared Weiss: Good morning. I'm Jared Weiss Associate Professor of Medicine at UNC Lineberger Comprehensive Cancer Center and Vice President here at Cancer GRACE. And it's my privilege today to speak to you on the role of liquid biopsies versus tissue biopsies. And with apologies, I'm going to slightly change the name of the talk to you, and tissue biopsy is to reflect a key point that these are ultimately complimentary. Here are my disclosures. None are directly relevant to molecular testing or the content I will discuss. So in 1995 I won't tell Jack what I was doing in 1995. Those working in the field had reached a relative plateau. We had shown that in moving from the yellow curve, which has no chemo at all to the white, which was the then modern chemo, that there was a survival advantage. And as we moved forward, another almost decade to more modern doublet therapy, the optimistic note was that these curves shifted upward from no chemo, to older chemo, to modern doublets.

The pessimistic point is that all of these nicely colored curves are pretty much overlapping. We have hit a therapeutic plateau. That impasse started to be broken with targeted therapy. You're looking here at a patient treated with gefitinib back almost 20 years ago now. And I would ask you to note the dates at the bottom. This is why targeted therapy is inspirational to all of us. This is five days, patient having dramatic improvement in cancer. And I think we all know from our practice or perhaps our own

experiences that the symptomatic improvement can be similarly dramatic and rapid. However, at the time that these radiographs were made, we didn't really know the underlying driver. There was this new drug gefitinib. And we started to get evidence that there were patients with certain clinical characteristics that were more likely to respond, but we hadn't yet defined mutations as we modernly define them.

Fast forward to about 10 years ago, and this this new drug this EGFR inhibitor gefitinib, was compared to the then standard of care, carboplatin paclitaxel. What you're looking at here is a progression free survival curve. It ticks downward every time a patient dies or their cancer grows. And the shape here is one that's famous to clinical trialists. There are a few explanations for why curves can cross over this way, but by far, the most common is that you have two discrete populations that you have not identified, one, benefiting more from one drug and one benefiting more from the other. And as we fast forward to the current day we know that if you give a patient without an actionable mutation, the relevant targeted therapy, it doesn't work, right. If we were to make an analogy to a lock and a key model, it would be like using the key to your house to try to open my door. It just doesn't work.

In contrast, when we give targeted therapy to the right target, putting the right lock in the right key, we have our aha moment where our less toxic, more convenient cancer pill, beats the pants off chemotherapy for efficacy as well. A theme that we've all become quite familiar with. Another theme I'm going to show you throughout my slides is blatantly stealing beautiful slides from my friends and colleagues. This one here from Joel Neil, you know, one of the problems of virtual presentation is I really can't see if you're laughing or if that completely flopped. So I'm just going to assume you're all losing it in laughter. But what Joel shows here very nicely regardless, is that we're discovering more and more actionable oncogenes and of the ones we know more and more of them are becoming actionable. This is a conceptually very important slide. What you're looking at here is slightly old data, but the core principle remains the same, even if median survival has happily shifted more favorably.

In the green, we have the best surviving curve here showing that if you have a, a dark green at that, excuse me, that if you have a driver mutation and you match it with the appropriate targeted therapy, patient lifts much longer, that's what we're all seeking here. But what's really interesting. Here are the bottom two curves showing that survival is the same between patients who either don't have an actionable oncogene or if that oncogene is never action. And that's the whole point of what we're talking about today, how to find an action in these oncogenes, continuing the theme of blatantly stealing the slides from my friends. This one is from the panel. And what Nate has nicely done here is showing the rates of EGFR testing globally showing in core that it is imperfect, seventy-five percent testing rate for EGFR in the United States. And as Jack

showed you very nicely in his presentation, as you get to newer and newer and rarer and rarer changes that testing rate falls off dramatically.

So, there's no chance to action and oncogene, if you don't find it a major, major problem, now, why do we not get testing? As Jack spoke about, there can be knowledge gaps around testing or about actioning. Limited tissue can be a major problem, particularly in some community settings. Biopsies can be small. Actually that's any setting biopsies can be small. We don't like to puncture the lung. And so our needles are often smaller. What's called fine needle aspirates, leaving us with less material further. Tissue can be used up during testing to show that it's cancer, that it's lung cancer. And the major problem is something that we call tissue stewardship, which is to say responsible use of limited tissue. I've seen massive panels used where really the clinical scenario, radiographic appearance, were screaming, I am lung cancer. The basic markers were screaming, I have lung cancer, and yet 10 or 20 special tests were done to prove that it wasn't something else.

And I've seen the comic extreme prostate cancer being tested in a woman who obviously had lung cancer. In many other practices though turnaround time is the biggest barrier. And I would cite my practice as an example of this. If you think about it, the time to go from the identification of a need for testing all the way to an answer can be quite long. It starts with ordering the test. The patient might have to see the provider who's going to do the test. They might schedule it a week or two later. Then once it's done there's a lot of processing that might need to be done. The pathologist called this pre-analytic variables, I call it nonsense. Or if I weren't in a public forum, maybe an explicative I hope that one had better than my prior jokes, but at any rate, the point is that even going from the acknowledgement of the need to test, to getting the tissue into a FedEx envelope to get to a molecular lab can be weeks of time. And then of course, these tests take time.

The time from initiation of the testing to final results, especially if you're using the most advanced testing with this fancy but useful Hardy fusion panels can then be several weeks. As mentioned, there's a lot of coordination involved in getting there. And there are reimbursement issues, particularly if multiple testings are done. So this slide is taken from Dr. Lovely who summarizing work done by our colleague Dr. Charles Agarwal, again, looking at reasons for lack of testing, insufficient tissue is commented a third of samples in her study, biopsy not possible, and 10%. I think that should probably be pretty rare. And so now finally getting to the main point here, what is a liquid biopsy? Well, we know that the nature of all cancer mutations, you have a once healthy cell in the human body, and it becomes a cancer cell through mistakes in it's instructions. Those instructions are called DNA, and the mistakes are called mutations.

Traditionally, we test for these by putting a needle into the cancer and studying that DNA, but cancer cells grow so fast that they naturally die even in the absence of treatment. And when they die some release DNA of sufficient quantities into the blood in a way that we can detect. And that's what a liquid biopsy is looking for these mutations in blood, the term is occasionally used to refer to testing and other liquid media such as the CSF in the brain, or fusions in the heart and the lung. But most of the time we say liquid biopsy, we really mean blood. Perhaps the most commonly used of these tests commercially, is the Guardant Health Test. I have no stock or arrangement with Guardant Health of any kind, but it also has perhaps the best data on the operating characteristics, how well these tests work. I draw your attention here to the fact that at first that most tests that are positive on tissue will be positive on blood and vice versa.

And that the concordance is also high. Most that are negative on one are going to be negative on the other, but highlighted in my red box this year is the interesting fact that some changes will be found only in tissue or only in blood, which is why I changed the name of this talk to reflect that these tests can be complimentary. This study looked at things from the gold standard being tissue. And when you look at it from that perspective, a change found in blood had a hundred percent positive predictive value. In plainer English, what that means is that if you find an actionable oncogene or molecular change of any kind in blood, you can believe that it's real. You're going to find it in tissue again, from the perspective of tissue as gold standard sensitivity was 80%, meaning that if there's a change present in tissue, you have an 80% chance of finding it in blood and critically from any practices, including mine with speed. By the end of the study, turnaround time was seven days. And with this and other commercial assays, the turn around time is often faster than that.

Further often can eliminate some of those pre-analytic variables, multiple of the companies will even send a phlebotomist out to the patient's home, which can further decrease the time. So what are the strengths and weaknesses of liquid testing? This biggest strength in the real world is that it can overcome limited tissue. In many practices, including my own speed matters. And these are fast. They can address clonal heterogeneity in plainer English, what this means is cancer at different places, having different characteristics. So when you put a needle into cancer, all you really learn about are the characteristics of the cancer, where you stuck the needle, but analogy here might be made to Darwin's finches. Darwin's finches evolved separately from each other on different islands. Cancer is very similar. Each spot is relatively separate from the others, and they can evolve different resistance changes. It is not humane to stick a needle into everything, but liquid gives you a shot at integrating and knowing all of the resistance changes that might be present.

And as I mentioned, I believe that it can be complimentary to tissue because each modality will pick out a few changes that the other will not. As mentioned before liquid tests are imperfectly sensitive, and that's probably the biggest barrier in real-world use. One strategy that multiple of the companies propose. And I think is reasonable, is to send off a liquid molecular test as your first test you can send off the tissue and just cancel it if you get a positive. So, in other words, serial testing, if the liquid gives you an answer, you have your answer. If it doesn't, then you still need a tissue. I think that's a reasonable approach, but I would note, again, the insensitivity in particular, for some of our newer changes that revolve around fusions or rearrangements of genes or amplifications. The reimbursement issues, I think I've touched upon already. A critical issue I have not touched upon is that liquid testing cannot look at protein based markers.

So, the test that we use to prove something as cancer, the tests that we use to prove that it's lung cancer really can't be done on a molecular test. There are some mutations that are more common in one cancer type or another, but there are really none that are totally pathomolenic for exactly one cancer type to prove what you have. And further PD-L1 has become an important biomarker for decision-making in immunotherapy while it is a very imperfect biomarker. I note that it can only be done on tissue. You can't do it on a liquid sample at the current time. At the time of progression on a targeted therapy, the cancer is acquired a secondary change. That's renders it resistant to the treatment that we're giving. There is some work showing that you can detect. Some of these changes with liquid biopsy is the advantages. This again, are that it's fast and that it obviates the need for tissue biopsy. The applicability of course of this is different in different contexts.

One idea that I find fascinating is the use of circulating tumor DNA or liquid biopsy in the adjuvant setting for Adjuvant decision-making. One of the most controversial new findings in lung cancer was the adjuvant osimertinib data shown at ASCO. In rapid summary. What it showed was a massive improvement in disease, free survival for three years of adjuvant osimertinib in patients with local or locally advanced surgically resected, EGFR mutated lung cancer. But that data has been extraordinarily controversial with multiple of your speakers today having commented on it, and the core of the controversy, there are probably multiple core controversies, but one that I'll highlight for you today is the concern that there may be some patients who derive, who are already cured at the completion of standard therapy for whom the TKI offers only toxicity and no potential to improve survival.

Heather Wakely and others have proposed the idea that the use of circulating tumor DNA might be used to adjudicate the patients at highest risk of recurrence who might be most likely to benefit from that type of therapy. And I look forward to seeing more data on this idea. I like to end most of my slides with a cute kid's picture. And so I end here with a picture of the twins, Dina, and Betty and one of Charlotte. And if you like cute kid's picture slide, I invite you to come back for my next talk later today on frontline EGFR where I promise two more pictures. I thank you for your kind attention.