CLL Society

Transcription: ASH 2016: Dr. Neil Kay: Mechanism of Ibrutinib Resistance in CLL

Brian Koffman, MD- I'm Brian Koffman. I'm a family doctor, turned CLL patient, and the Founder and Medical Director of the non-profit CLL Society.

Neil Kay, MD - Hi, my name is Neil Kay. I'm a staff hematologist at Mayo Clinic, and most of my work is in Chronic Lymphocytic Leukemia.

BK - Dr. Kay, Ibrutinib has been a game changer in CLL, but it doesn't work for everybody, and it doesn't work forever for people. So, there was some interesting data presented here out of Ohio State on how that resistance develops. Can you help explain that at a patient friendly level?

NK - Sure, I'll do my best. So, I agree entirely with you, Ibrutinib now is approved for up front use, as well as for 17p CLL patients. There is a growing cohort of patients who are on that signal inhibitor. The response rates are very high at 90%. And even though these can be very durable responses, ultimately there are two main issues. The one is intolerance, which unfortunately does occur in a subset of patients, but the other is patients do become drug resistant and through the work at Ohio State where Amy Johnson and Jennifer Woyach initially published in the New England Journal a few years ago, in a small cohort of patients, I think six, that there were two individuals who were resistant to Ibrutinib because they had a PLC gamma 2 mutation which is downstream of the BTK, and then actually four who had mutations in the BTK region, at c481 serine.

BK - And my understanding is, is that if you have that mutation in the c481,

NK - Yeah.

BK - Then the Ibrutinib can't bind, and if it can't bind it can't block the pathway, and if you have the pc gamma 2 mutation that turns the BTK pathway on again. It's a gain of function and it's downstream, so even if the Ibrutinib is blocking, it's being turned on again.

NK - Exactly, that's well explained. And essentially what you now have is, if you will, atonic signaling of the BCR pathway, even in the presence of Ibrutinib.

BK - It's like the Ibrutinib isn't workin'.

NK - It's working, but it's more of a competitive inhibitor and not a non competitive

BK - Okay

NK - inhibitor. There's a rational and a mechanism for why patients do become resistant. What was reported, this year, which I think was very helpful, was they expanded their series of CLL patients who are on Ibrutinib and they did, I think what's a very meritorious thing, they studied using deep sequencing, deep genetic sequencing so they could pick up even very small numbers of cells who had mutations that might relate to resistance. And a couple of things that are worth pointing out. First is, it still looks like the majority of patients who are going to become resistant have the BTK or the PCL gamma 2 mutations. There's a little bit more of a

spread in terms of where the mutations might occur, but nevertheless it's in those domains. What also is interesting is that they're finding the emergence of these mutations, sometimes months before the relapse, the clinical relapse occurs. And, so, there can be, if you will, a biomarker now for individuals on Ibrutinib who look like they're going to relapse. And there are some very important reasons why that we need to know that. For one, of course, we ultimately believe that almost all will relapse, although we still don't know the whole story about that. The CLL B-cell clone may be under a controlled, beyond just its own proliferative rate, there may be immune regulation of the clone, and so on, but, probably a majority of those individuals will relapse. If these individuals relapse unexpectedly we now know that their disease can be quite explosive. Where if the Ibrutinib is stopped suddenly there will be a rapid proliferation and clinically it can be a serious issue. So, having that information allows us to counsel the patient, to watch the patient perhaps a little more carefully, a little more closely, and try to come up with a plan for treatment when ultimately they do have that clinical relapse that requires new therapy.

BK - And fortunately we heard today that there are plans that are available,

NK - Absolutely.

BK - So, Dr. Jones talked about using Venetoclax with that, I think a 70% response rate for patients just like this.

NK - Yeah, I actually had two abstracts. One with Venetoclax as a single agent, and then the triple combination where they used a very innovative regimen, Obinutuzumab to kind of debulk, and then added Venetoclax and the Ibrutinib, in sort of, in sequence, and that also looked very encouraging, although they haven't put a lot of patients on it.

BK - Right.

NK - They didn't report the outcomes, but there are clearly going to be, if you will, rescue opportunities with these drugs and others. I would be very optimistic that given the depth of research that's going on in signal pathways, that there'll be even more than those two or three that could be used.

BK - And this is obviously an issue that's close to my heart, as I'm going through these concerns. But it's, I think one strong argument for being in a clinical trial, because when you're in a clinical trial, these are tests that are not generally commercially available, or not at all commercially available. But when you're in a clinical trial, people are watching for these things, and this is an argument to look at clinical trials, because I think the clinical trials watch you more carefully and you can see into the future a little bit better.

NK - You and I see eye to eye on that. We need to have as many patients on clinical trials as possible. If that is not feasible or possible in this current world of medical therapy for CLL, the opportunity to have genetic testing for these mechanisms are paramount. They should be available. And, again, it's primarily because we wouldn't want to have a patient suddenly have

to come off it where there's no planning for the reasons I stated earlier. So, I would hope that there will be a CLIA-approved drug test that's available to do this genetic testing.

BK - That's commercially available.

NK - That's commercially available, yeah.

BK - Right, any final thoughts on this?

NK- On the resistance mechanism?

BK - Right.

NK - Yeah, we know more, and actually we may know a lot more about the story for resistance mechanisms in Ibrutinib, but these other agents, Venetoclax, Idelalisib, those also require studies, too. And it's one of the reasons I'm with you in terms of clinical trials, where we're doing correlatives, looking at clonal evolution, clonal architecture, the drug resistant mechanisms that occur. These signal inhibitors are powerful, but they also have potential, they are potentially powerful in mediating genetic changes that we would not want.

BK - Alright, Dr. Kay, thank you.

NK - Thank you very much.