How Does Genetic Testing Affect CLL Treatment Options?

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Andrew Schorr:
So let's talk about some additional kinds of testing that we in CLL have been hearing about now. So, Dr. Kipps, FISH testing, okay? So—or the various kinds of tests to look at the character of our CLL, which I understand can change over time. So, for instance, I don't claim to understand this, but I think, I don't know if I was 13q 11 this, whatever, and I know that some, I've heard it said that 17b—p can be more aggressive. So where—what tests for that, and where does that fit in with your decision-making or recommendations?

Dr. Kipps:
Well, the FISH analysis that you mention stands for fluorescence in situ hybridization. That's a big term, but what specifically is being done is we have the cells put out on a slide, and then we have probes that can identify discrete areas of the genome and they can actually paint chromosomes in certain areas. And these probes then look for regions that are commonly deleted in patients with CLL.

And so over time and experience looking at a number of cases we've been able to hone down the areas that are most commonly altered to a few basic areas, and so by using these probes to paint the cells we can then look at the cells and count the number of paint spots to indicate whether we're missing that part of the chromosome in that cell.

And so basically it's a somewhat labor-intensive technique. Typically, what we score is 200 cells that are painted with these probes, and one can determine whether there's a deletion in one or more arms of the chromosome, and we can also tell whether there's an extra copy of a chromosome. Now, the P and the Q, what they stand for—you got to know your Ps and Qs—the P stands for the short arm of the chromosome, and the Q stands for the long arm of the chromosome.

As you can see, sometimes chromosomes have very short arms and long legs. The long legs would be the P part—or the Q part, rather, and the short arms would be the P part. So when we talk about deletions in 17p what that means is that a probe that looks for this region in the short arm of chromosome 17 is either not detecting it on the cells so that they may only have one instead of two spots. You know, you know, you have one chromosome bunch inherited from your mom and one from your dad, and so you should have two copies of each chromosome in each cell.

And if you paint and find only one copy there and the other one a missing, then you say you have a deletion in that region. And sometimes you can have deletion in both. In other cases where you may look at, say, chromosome 12, we oftentimes may find patients with an extra chromosome 12. So instead of having one copy from your mom and one from your dad you may have two copies from your mom and one copy from your dad, and therefore have three copies of chromosome 12. That's an abnormal, and we then score that as well.

Andrew Schorr:
That's trisomy 12.

Dr. Kipps:
Trisomy 12, trisomy meaning three of the chromosome. Now, these probes that we look at areas in chromosome 17, short arm, chromosome 11 at the 11q, which is the long arm of chromosome 11. We have trisomy 12. Some labs look at the chromosome 6, the long arm of chromosome 6, and as well as the long arm of chromosome 13 are the commonly used probes. And what we do is you look at the cells, you find two copies of each probe in each cell and you count 200, that means we haven't detected anything. Does that mean that there are no abnormalities? No, we've only looked for those abnormalities that are commonly found to occur.

Andrew Schorr:
Okay.

Dr. Kipps:
And so that's important to note. We have another test that we do in addition to the FISH, and it's something we've adopted with the Mayo Clinic and the Ohio State University as part of the CLL Research Consortium, and that's something we are doing in our genetics lab. We got everyone together at one time, and we decided to work on doing what's called a metaphase analysis.

And what that means is to try and look at all the chromosomes to see if they're all there, whether there is any alteration or missing chromosomes, and you can see that this would be a lot more sensitive, because it could detect abnormalities other than the most common ones. But unfortunately since it's so labor intensive we typically can only score about 20 cells and not 200 cells. So the sensitivity lags for that reason.

And what we have learned is that we can stimulate the cells prior to doing this analysis with a cocktail, and it stimulates the cell and it makes it more apparent changes in the chromosomes that we wouldn't see otherwise. And I would encourage all labs to do this. I'm not sure all the cytogenetics labs are doing this. They're not doing this analysis, but I think it's very useful, metaphase analysis looking at the actual chromosomes.

And we found that some patients may have a lot of changes which may not show up on the FISH analysis. And I was a little bit remarked on this when I first saw this. We thought maybe we were inducing these changes in the laboratory, you know, because you're putting cocktails to stimulate the cells.

So we did a test here. We had patients in our clinic that we found that had these changes, and I got blood samples as part of an informed consent study. We sent blood samples to Mayo Clinic and Ohio State and to Dana-Farber and to Long Island Jewish, and we had them do this sensitive test, and each of them came back to report the results, and each lab, including our own here, had the identical changes. And so I think it's a real change that occurs in our bodies that we should know about it.

Now, if we see three or more of these chromosomal abnormalities, we call that a complex karyotype. And one rule of thumb about genetics—it's better to have simple genetics and not more complex genetics. I think it's important.

Now, these studies are very helpful for us particularly before we are looking at treatment. They are less useful in the time we have if it doesn't appear that treatment is really in the cards for the foreseeable future. As you mentioned, there can be changes over time, and I would like to know what these genetic alterations are, if any, prior to making treatment decisions of what would be the best type of therapy, what sort of therapies do we need to avoid.

And if we get it when we are just waiting, they don't seem to much influence the tendency for progression of the disease, although some are associated with more rapid progression. But there are other markers that they are associated with that are perhaps more reliable indicators of that that we typically use to try and define what the risk of clinical progression is.

But let me put it this way: Nothing beats good, common, clinical sense, and actually seeing the patient, examining the patient, trying to assess the lymph node size as best you can, looking at the CBC and interpreting, as Dr. Susan Leclair said earlier, I think we have to understand the noise that might be there and look at the big picture, where are we headed. Is the disease progressing, are there symptoms that we can ascribe to the disease, and use that as tools for defining when a patient best should be treated, because really that's caring for the patient and not getting caught up on some crazy test.

Andrew Schorr:
I mean, we got into FISH testing and metaphase and all this stuff and say, oh, my God, does my lab do that? But Dr. Kipps just brought it back to hands on the patients. How are you doing? How do you feel? Are you having night sweats? Are you getting to do what you want to do? Do you have bulging lymph nodes, right?

Dr. Leclair:
Right. The key to all of medicine is the relationship between the physician and the patient, and that requires—hmm, now I'm out numbered in gender here. And that requires the commitment on the patient's part to not use the word fine as in, no, I'm fine, when that really means well, I'm fine, except I fell off my bike yesterday, and that's the reason that my white count went up three times the amount it was before. Or, no, I'm fine, yeah, occasionally I have night sweats, like nightly. So—see, see, you're laughing, and that is probably the single most important thing.

I worked with one physician once who said, if you have the time, and he listed about an hour to an hour and hour-and-a-half, a good physician can accurately diagnose pretty much almost anything in just listening to the history and doing a targeted physical based on that. We can't get away from that. We can't lessen the importance of that.

Yes, the lab tests, I obviously think are critically important, and they do make life easier in terms of providing information upon which you can make decisions, but you can't get away from that conversation in which you have to say, yeah, I haven't had night sweats in six months, but the last three nights I have. Well, maybe then we should possibly look at that CBC sooner than anticipated. That's where that comes from.