What Tests Are Used to Categorize and Treat CLL?

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Andrew Schorr:
So John writes in, please compare purpose and benefit differences for FISH testing versus next-generation sequencing. So maybe you could explain them too.

Dr. Sharman:
Absolutely. Thank you for the question. It's one that I think is often very difficult to comprehend.

So a little bit of history here is that we've known for a long time with that patients with chronic lymphocytic leukemia have a pattern of common chromosome gains or losses, and we generally pay attention mostly to five separate categories.

There are some others that people sometimes look at, but ranging from sort of worst to best, worst is having a loss of chromosome 17p and P stands for petite arm, so part of the short arm of chromosome 17 is lost. 11q, Q stands for the long arm of chromosome 11. And then you have normal chromosomes or the addition of an extra chromosome 12 or the loss of a portion of chromosome 13 that kind of goes from worst to best. And that is very different than actual mutations in genes. So these are wholesale losses of large clunks of chromosomes.

And if you look at 17p the reason that 17p is bad is because there's a particular gene there that's very important called TP53, and you can actually have a mutation in TP53 without the presence of a chromosome loss. And so next generation sequencing looks at a host of additional genes that really until the last three to four years we didn't know have the significance that they have. So TP53 is probably the most important, but you're also seeing things such as SF3B1, NOTCH1, FA1. There are a variety of them that are out there. Some are better understood than others, and I think to some degree we're still as a field even trying to figure out how best to integrate these into our clinical practice.

Andrew Schorr:
Okay. So would you recommend for the typical CLL patient that they have FISH testing, which tells you about the chromosomes, right?

Dr. Sharman:
Yeah.

Andrew Schorr:
And when do we need to do genomic testing to see with whether if any of those genes you just rattled off?

Dr. Sharman:
Yeah. So I can tell you about my own personal practice on that. I do think that the field, as I indicated before, is still trying to digest this, and a number of those specific mutations there isn't necessarily super robust consensus as to when is the best time to draw those. So I'll explain how I've thought through it, and if that resonates with you.

So my question in the previously untreated patient is whether or not this patient is suitable for chemoimmunotherapy. Previously I said appropriately selected patients get very long duration responses. I don't want to give chemoimmunotherapy to a patient who is not going to get a sustained benefit.

If I anticipate that I'm only going to get 18 months benefit or two years of benefit, it is not worthwhile in my mind going through the chemotherapy to get that. I would rather put those patients on a tyrosine kinase inhibitor.

So my first stratification is the IGHV mutation status, and I would say in general if somebody's mutated, which is the more favorable form, I would tend to err more on the side of chemoimmunotherapy for those patients. For those who are unmutated, which is the bad one, I would tend more towards targeted therapy. These aren't totally black and white.

But my next level of stratification is FISH. So if you've got a bad FISH finding even if you're in that favorable category I strip you out from the chemotherapy group.

Andrew Schorr:
So like if you had a 17p deletion, those chromosome deletions?

Dr. Sharman:
Yes. So if you're mutated, which you think is good, but you also have a 17p, then I wouldn't give that individual chemoimmunotherapy.

So if you have good IGHV, good FISH, good functional status and I'm thinking about give you FCR, that's my final check is let's make sure there's not something lingering underneath the surface here that I don't know about. So that's where I check it.

Now, in the relapsed/refractory setting it is more the norm that those patients are almost all going on novel agents where those mutations are sort of a little bit less salient, so I don't necessarily check that. However, I do recheck FISH with successive lines of therapy because that certainly can evolve. And to make things even a little bit worse now for somebody who has been on BTK, we need to think about BTK mutations and whether or not that patient might be suitable for a second- or third-generation BTK inhibitor that can get around that.

Andrew Schorr:
Okay. And the genomic testing, when do you do that?

Dr. Sharman:
Well, so genomic testing is looking for those smaller mutations that don't show up on FISH.

Andrew Schorr:
Okay.

Dr. Sharman:
So that's my final break point before I would give somebody chemoimmunotherapy. But I will tell you, there are opinion leaders out there who will argue that chemoimmunotherapy is dead and shouldn't do it.

Andrew Schorr:
Right. There are.

Dr. Sharman:
I'm in the camp that thinks there's still purpose and value in doing that in appropriately selected patients.