Defining High-Risk Subgroups of CLL

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Andrew Schorr:
And just to define, you said high-risk subgroups. So, today, what would test results be where you'd say to the patient, "You may be in a higher risk subgroup." What would that look like?

Dr. Brown:
Well, I think we would say that about 17p deletion, or TP53 mutation. Other than that, it's not completely clear. They are not good prospective data, really, addressing the impact of these individual mutations. NOTCH 1 mutation, I think, does worry many of us because it has been associated with Richter's transformation in several studies, and we don't really understand the biology of that yet. And so, that, I think, is something that many of us would like to understand so that we can address that and try to prevent it.

But it's not something that we understand well enough to say that we should change your treatment based on this, or that we even know will ever impact on a person. It may just be there for years and not have an impact. And so, it's important not to over-interpret the results at this point.

Dr. Wierda:
So, just one other thing I would add to what Jennifer was saying in terms of high-risk patients. We didn't spend a lot of time talking about it, and Jennifer did mention it initially. And that is metaphase karyotyping, or stimulated karyotyping. This is a gross way of looking at the chromosomes, and it's a way to survey all of the chromosomes in a single cell. And you need to have the cells dividing in order to generate this karyotype. And a complex karyotype is associated with a high-risk—with the treatments that we have: venetoclax (Venclexta), ibrutinib (Imbruvica) and chemo-immunotherapy.

High-risk is associated with a complex karyotype, so that's three or more abnormalities in a single cell. And so, those are patients that I would watch closely in addition to the patients with an 11q, and a mutated TP53. So, in terms of the most important features to know, 17p, you need to know, and whether or not TP53 is mutated, you need to know. That's for everybody. For patients who are younger, and fit, and you're thinking about giving them potentially curative treatment with FCR, you need to know if they have a mutated, or an unmutated immunoglobulin gene.

If they have a mutated immunoglobulin gene, then our recommendation is for FCR-based therapy. If they have an unmutated immunoglobulin gene, we're not giving those patients chemotherapy any longer, we're using the small molecule inhibitor-based therapies in preference to chemo immunotherapy. Because, we know most of those patients, disease will come back with standard treatment with FCR.

And we'd rather spare them exposure to chemotherapy in preference to the newer small molecular inhibitors, and try to minimize their risk for complications that you can get with chemo immunotherapy. So, 17p, mutated TP53, and for younger, fit patients, immunoglobulin gene mutation status is important to know.

Andrew Schorr:
So, what would be the questions, just so it's very clear that people might go to a community oncologist. What test would they be seeing? I just want to make sure because, you named – there were certain tests named out.

Dr. Wierda:
FISH test for 17p, mutation analysis for TP53. And then, for the younger, fit individuals, immunoglobulin variable gene sequence analysis. Those are the three tests that I would recommend doing.