Clinical Trial Updates on CLL Patients With Genetic Mutations

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Andrew Schorr:
There were a lot of studies coming out, so what else, Jeff?

Dr. Sharman:
I would actually say this is the year for CLL. I've been coming to ASH for 15 years or so, and every year sometimes it's good for one cancer. And other cancers, there's not a whole lot new, and you get back to your practice and people say what's new? CLL has had a great year, and to echo Nicole's comments, a lot of questions have been answered regarding correct frontline management of CLL. To sort of piggyback from what you said, when we do clinical trials, there are different goals of why you do a clinical trial. Sometimes it's to answer what's the best way to do something. Sometimes you're trying to answer can I get this drug approved and get access to patients?

And so, one of the studies that had been out there for a long time was ibrutinib (Imbruvica) versus chlorambucil (Leukeran). I almost kind of feel like that study was verging on unethical. I think we knew what the results were gonna be, and you want some measure of equipoise, some uncertainty like you might not necessarily know what the outcome's gonna do. That's why you do the experiment, but ibrutinib had never been compared to what we would call real therapy and chlorambucil sort of being almost not a real therapy. So, bendamustine, rituximab (Rituxan), fludarabine (Fludara), cyclophosphamide (Cytoxan), rituximab, really the regiments you have been using over the last 10 years to say, oh, we're gonna get your CLL under remission, this now puts in a real clean head to head situation.

When you do that, there are a lot of sub-questions you can answer, and you were talking about maybe there's some subgroups and so forth. I don't want to get too technical, but I think there's value in highlighting some of these, because I think you've got a pretty sophisticated audience. One of the big dividing lines in CLL is whether you are what we call mutated or unmutated. It has to do with what we call the B-cell receptor. Sometimes you see it referred to as IgVH mutation analysis, but the patients who are mutated tend to have better outcomes. The patients who are unmutated tend to have less good outcomes. When I say less good outcomes, the chemotherapies can still get the disease into remission, but oftentimes those remissions aren't as long-lasting. So, I think it's very clear that novel agents, such as ibrutinib in those patients who are unmutated, it's hard for me to justify using chemoimmunotherapy in a patient who's got un-mutated B-cell receptor.

Dr. Lamanna:
Agreed.

Dr. Sharman:
Conversely, in the mutated population the question is those patients are going to oftentimes get a better response to chemoimmunotherapy than their unmutated counterparts. So, there may be a closer approximation there. There are two main frontline studies: ibrutinib-rituximab versus FCR, and then ibrutinib against BR versus ibrutinib-rituximab. We

haven't seen the ibrutinib-rituximab versus FCR. That comes out tomorrow morning, but really in all groups, advantage ibrutinib. Who would you give FCR to anymore? Boy, that's a small group of very young, very fit, very robust patients who are committed to a short duration therapy who have the most favorable molecular features. That's the only group where I would use it.