An Expert's Review of CLL ASH 2015 News

Wiliam Wierda, MD, PhD
Medical Director, Department of Leukemia, Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center

Andrew Schorr:
Hello and welcome to Patient Power. I'm Andrew Schorr. At the recent meeting of the American Society of Hematology, the 2015 meeting in Orlando, There was a lot of discussion about CLL, chronic lymphocytic leukemia. We got the perspective of a leading CLL expert, Dr. William Wierda from MD Anderson and what he had to say about the latest research.

Dr. Wierda:
Where we're at right now with regard to treatments for CLL is that we're in sort of a tornado of activity, and new drugs are being developed or have been developed or being approved. There's a lot of data coming out this meeting. Particularly, there's probably more data that we've had come out than in many prior meetings. So, for example, the RESONATE-2 data will be presented at this meeting, so there's a lot of change that's occurring. The standard of care is changing, and there are new drugs and new strategies that are becoming available that we haven't had that are becoming available that we haven't had in the past.

It's a very exciting time for CLL. It's a challenge, because I think it's upon us to sit and discuss and decide what do we really want to achieve for our patients. Probably it's not the same for all patients, and having a more patient-centric or personalized approach to management would be the best approach and direction that we're going. For example, for a first-line therapy for a patient who's 65 who is relatively fit, the objectives and what you want to achieve and what the patient wants to achieve is gonna be a little bit different or quite a bit different than say a 75- or an 80-year-old who has some symptoms. But we want to control their disease and not worry so much about five-, 10-year long-term outlooks.

Andrew Schorr:
In my interview with Dr. Wierda, I went on to ask him about genetic testing and how it can help patients gets the right treatment at the right time.

Dr. Wierda:
So the prognostic factors are important right now. The FISH is important, and FISH is important to be done when patients need their first treatment and also when patients need subsequent treatments when the treatment that they're on isn't working or when their disease has come back after a period of remission. It's very important to recheck for chromosome abnormalities by FISH, because patients can acquire new chromosome changes. The FISH is the single test that will help us direct treatment among all the laboratory tests that we can do. There are a number of prognostic factors that you can evaluate for patients. They are informative.

They tell us how the disease might behave, but they're not necessarily useful in directing therapy. Immunoglobulin V-gene mutation analysis is an important test for our clinical trial purposes. It is directing treatment, so for example, for patients who don't have a 17p deletion but have an unmutated V-gene for example., and they're needing their first therapy. Those

are patients that we're developing clinical trials that are utilizing non-chemotherapy agents so that we can manage and control the disease for hopefully extended periods of time and delay exposure to chemotherapy so that we are not worried as much initially about the toxicities and the toxic effects and the bone marrow damage that you can see with the chemotherapy.

And that's in contrast to patients who are young, fit and have a mutated V-gene where we know those patients if they get in a good complete remission, and they're MRD negative, they may be cured from their CLL. These are patients in our experience with FCR who we've gotten into remission, and they've remained in remission more than 10 years, and they're continuing in remission. We just reported our long-term follow-up from the FCR, initial FCR, clinical trial. There are a fair number, two-thirds of the patients with a mutated V-gene, are in remission beyond 10 years.

So right now FISH is very effective and useful in directing treatments particularly in the community for the research objectives that we have for sure FISH is very important. But mutation status is also becoming important.

Andrew Schorr:
And so, of course, a lot of CLL patients are on a fairly newly approved therapy, ibrutinib or Imbruvica. But there are some patients where it's not right for them. They have trouble with side effects, and so there's a lot in research. Maybe they can move on. What's the latest on new agents for CLL?

Dr. Wierda:
Well, as you say, for the drugs that we have approved, for example, ibrutinib, idelalisib (Zydelig), there are patients who go on those drugs. They are extremely effective drugs that are controlling the disease, but patients do have to come off treatment occasionally for side effects. And they're generally drug specific, so the side effects that you'll see with Imbruvica are different than those that one would see potentially with idelalisib. There are newer drugs that are in development, and clinical trials are ongoing that are in the same category with respect to the mechanism of action but may not have the same profile, toxicity profile.

So right now we have Imbruvica, which has its specific associated side effects. And if patients have to come off for those, they're not overlapping necessarily with the toxicities that you see with idelalisib. So idelalisib is the next reasonable rational choice today. Tomorrow or in the future that may change, because we may have Imbruvica. And you have a patient who is doing very well on Imbruvica, they have an Imbruvica-related side effect there may be another BTK inhibitor available for those patients that would not potentially have the same side effect profile as Imbruvica that would be an option.

That's probably in a few years, in a couple years, because obviously all of the clinical trials need to be conducted in order to get these newer agents that are effective approved by the FDA. And we have other new agents, for example, venetoclax, that are in a whole different category, with regard to mechanism of action, also a different side effect profile that different mechanism of action, which is hopefully gonna become the next alternative therapy.

Andrew Schorr:
Dr. Wierda now tells us about venetoclax, a promising new agent and how it could be used alone or in combination.

Dr. Wierda:
So venetoclax is an oral agent that blocks a protein called Bcl-2. Bcl-2 is expressed in high levels in CLL cells. It's a protein that is responsible for prolonged survival of the CLL cells, so venetoclax will block and down-modulate the activity of Bcl-2, and the cells drink away apoptosis. And so we've been involved in a number of trials with venetoclax. The first trial was a monotherapy trial with a dose escalations strategy. And that is in the process of being published, so we'll have data for that trial publicly available. It's been reported in meetings in the past, but we'll have the final report out very soon.

There have some other trials that have been combinations with venetoclax, for example, rituximab (Rituxan) with venetoclax that's been reported for previously treated patients. But this is an oral agent. It's taken once a day. There is some GI toxicity that's been reported, but it's very low grade. It's not treatment limiting. Probably the treatment limiting side effect that we've seen is regard to tumor lysis syndrome, because the drug is very potent—so potent that it will cause very sudden and extensive CLL cell death.

There are a lot of electrolyte abnormalities that can occur if that happens, so we have to be very cautious about starting at a very low dose and escalating the dose gradually to the dose that we want the patient on as the treatment dose. So that's

been the biggest challenge with regard to this drug. It's a good challenge to have, because the drug is so potent. The drug is very active. It doesn't have the same side effects as chemotherapy for sure, the same long-term toxicities that we worry about. It's very well tolerated, and patients are getting very good deep remissions with venetoclax by itself. So it's an agent that we're very excited about.

I'm hopeful that it will get approved in the near future. I think with regard to what I think people should know, patients should know and physicians should know is that it is such a potent drug that we have to be very careful and be very protective of the drug and be very cautious about how we use it so that every patient that gets it is that it is given safely to so that we don't have complications, because people are not as cautious as they should be when the drug gets out into the community, because we would not want to be in the situation where a drug is pulled from the market because of safety concerns.

Andrew Schorr:
Thanks to Dr. William Wierda from MD Anderson Cancer Center for joining us once again on Patient Power and sharing his perspective on the latest news and research. Be sure to be part of our community, so you'll always know whenever we post something new. I'm Andrew Schorr. Remember, knowledge can be the best medicine of all.