Therapies in the Pipeline for CLL

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Andrew Schorr:
Where are we with newer drugs in the class?

Dr. Lamanna:
There are, obviously, many that are being evaluated, and as you noted, one was just recently approved. Clearly, we're hoping, and we're still waiting on some randomized data. Many of these have been randomized head to head with ibrutinib (Imbruvica). So, we're waiting to see that, A, obviously, we believe these agents will have the same responses to ibrutinib, but will they have less side effects? And will the side effect profiles be better? That being said, obviously, there are many patients and many of you may be on ibrutinib. If you're doing well, then you're going to likely just continue ibrutinib, because you're doing well.

But there are many patients who do come off for side effect reasons, and those are patients who might be able then to switch to one of these second generations, so to speak, that may have less side effects or to an alternative B-cell receptor agent as well. So, maybe even a PI-3 kinase inhibitor. I guess the advantage is ibrutinib's first to market, fantastic drug, but clearly, if we can improve upon the side effect profiles of even the readily available agents and they have less side effects, that gives opportunities for patients to have more than one agent available to them, which is fantastic.

Andrew Schorr:
Jeff, there's a really strong pipeline in CLL, isn't there?

Dr. Lamanna:
There's a really strong pipeline.

Andrew Schorr:
You're both involved in research. Does that mean that if this drug, we develop resistance to it, there may be another way around it to go not that cancer cell on the head, or there may be a slightly different molecule on the same class that works better for us?

Dr. Sharman:
I would answer that by at least starting with the discussion about acalabrutinib (Calquence). Acalabrutinib is not approved in CLL currently but is approved in mantle cell lymphoma. And some of our professional guideline societies suggest that if a patient is having side effects on ibrutinib that would make you think to stop that patient, that may be a patient suitable for ibrutinib.

Andrew Schorr:
Acalabrutinib.

Dr. Sharman:
Yeah, acalabrutinib. And on the basis of that endorsement in what we call the NCCN, National Comprehensive Cancer Network, we can oftentimes get access to acalabrutinib for such a patient even when it's not approved. I would say the vast majority of patients do just fine on ibrutinib. In the frontline study that we saw in the plenary session, we saw that at the three-year mark, about two-thirds of patients were still on the ibrutinib. That raises the question about that other third. Some of them are for either disease progression, but there are a number of patients who stop for tolerance issues. I would hate for patients to stop for tolerance issues and not switch to acalabrutinib or at least try it.

My own experience has shown that some of those patients can do just great on a different one. Now there's a second issue, which is not if it's an issue of tolerance. It's a what happens if this drug stops working? And the most common reason that we see a drug such as ibrutinib stop working is actually a change in the BTK protein. It says 41-Searing mutation. It's a very specific mutation in the protein, and to your point about pipeline, there are now drugs in development that can bypass that mutation and potentially restore the benefit of going after BTK even when that mutation. If you have that mutation, acalabrutinib is not going to do anything good for you. Zanubrutinib is not going to do anything for you, because they all work at the same binding site.

Esther Schorr:
So, that's the justification for being retested if one drug?

Dr. Lamanna:
And because now we can test for these mutations. So, if somebody is really failing a BTK inhibitor like ibrutinib, you can test for this. And that would be important information because like Jeff was saying, you might be able to then switch to a more novel that circumvents this mutation and be able to then still be on a BTK inhibitor. And when we think about, which is a whole other can of worms, when we talk about how do we sequence these drugs? When you go from chemoimmunotherapy or combinations and how to get longevity, what we're trying to do is, obviously, provide patients with having a good quality of life, great response. We all want to cure the disease, but if these agents aren't cured of yet, how do we make sure that we can then go from one agent to another agent to another agent and keep you guys 22 years later doing what you love to do?

This is really important when we take this going forward. Like as Jeff suggested, it may not be switching all together if you can go from ibrutinib to acalabrutinib because you had a side effect, but you could still then go to acalabrutinib versus something else if you're not progressing. I think these are all very relevant questions.