Will Resistance Become a Problem for New CLL Drugs?

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Jeff Sharman, MD
Medical Oncologist
Willamette Valley Cancer Institute and Research Center

Andrew Schorr:
Hello and welcome to Patient Power. I'm Andrew Schorr. We're on location in Cologne, Germany, where experts from around the world in CLL are gathered, and they're discussing among other things the latest therapies, some that are quite close to approval. One of the things that has come up is possible resistance to one of the new drugs.

To help us understand this is Dr. Jeff Sharman. Dr. Sharman, from US Oncology, thank you for being with us once again. Tell us what you're seeing, what's being reported here about resistance, and whether this might be significant in CLL.

Dr. Sharman:
So I'll throw out a biologic term that we use in research, oncogene addiction. And oncogene addiction is a term applied to the addiction of cancer for certain signaling pathways. And in the disease chronic myelogenous leukemia, CML, which is very different than CLL, there is one protein that's mutated, the BCR-ABL protein, and that protein provides all the growth signals for that cancer.

There are drugs that inhibit that protein and do so very effectively. Imatinib (Gleevec®) was the first one, and then came nilotinib and Tasigna®, which is nilotinib and dasatinib (Sprycel®). And those two drugs are more powerful and so forth, but what was identified over time is that patients could get mutations in the BCR-ABL protein that would allow the CML to escape the Gleevec, or the imatinib. In some cases, those newer drugs were able to recapture it, in some cases they weren't, and now there are drugs in CML that are effective when all those drugs are ineffective.

So that's a lesson in oncogene addiction, and what we're starting to see in CLL, chronic lymphocytic leukemia, is some of the same story. So ibrutinib targets the BTK protein, which stands for Bruton's tyrosine kinase, and a small number of patients have been identified that acquire mutations in ibrutinib at the exact location where ibrutinib (Imbruvica®) binds to the enzyme, and so the drug is rendered ineffective. It cannot stop the enzyme from signaling, and so in some cases, yes, this does appear to be the case.

It also appears that in some cases if it's not the BTK protein that's mutated, something further down the signaling cascade, such as PLC-gamma, which is sort of the next-door neighbor in this signaling cascade can acquire mutation. And in that case, it doesn't matter if you're inhibiting BTK or not, because it's activated downstream of BTK. Now, it may very well be that adding a drug such as idelalisib, which is yet further downstream, may recapture the sensitivity, but at this point we don't know if that's the case.

And if you think about the chemotherapy experience, people are very familiar with 17p deletion, which is essentially a chemotherapy resistance marker. So it's not necessarily a new story. It's merely that when you're a child, you have a sore throat, you take antibiotics and the doc says, take your antibiotics all the way through so you don't get resistant. Whatever

that antibiotic is there [are] ways to get resistant to it, whether that antibiotic in this case is chemotherapy or whether it's one of these new targeted therapies. And I think the field is going to be looking at combinations of therapies and so forth to try to minimize that.

Andrew Schorr:
Okay. Dr. Jeff Sharman, thank you for explaining that. We'll stay tuned to see how all this plays out.

On location in Cologne, Germany, I'm Andrew Schorr. Thank you for joining us. Remember, knowledge can be the best medicine of all.