Combining CLL Treatments

John Gribben, MD, DScn, FRCPath, FRCP FMed
Professor and Consultant Medical Oncologist
Barts and The London School of Medicine and Dentistry, Queen Mar, University of London

Constantine S. Tam, MBBS, MD
Consultant Hematologist, Division of Hematology and Oncology
Peter McCallum Cancer Centre

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

Andrew Schorr:
So you're finding characteristics of the CLL. Like we used to know—I knew I received rituximab (Rituxan), which was an FCR, and it targeted a protein on the cell and hit it. And it was like a bomb, and it blew it up, and it did good for me—not everybody but for a lot of people.

But now you're understanding other things that are fueling the cell, right? And you're trying to cut off these sort of power—things that power it, an escape route story?

Dr. Wierda:
Cut off the fuel supply.

Andrew Schorr:
Yeah, cut off the fuel supply. All right, so is the idea, just like we had with FCR, that if you combine medicines, the cancer in a sense can't escape. Bill, do you want to talk about that?

Dr. Wierda:
Sure. That's the rationale behind combining these agents and targeting different mechanisms at the same time that our survival signals, for example, for the cell so if you block BTK and you're blocking Bcl-2, for example, then you're hitting the cells. These drugs don't have overlapping toxicities, necessarily so you can—patients will relatively well tolerate them together. The CLL cells have less of an opportunity to develop resistance and to survive that double hit of toxicity to them.

Andrew Schorr:
Let me just follow up on one thing about that resistance. So we've seen in some other conditions a concern where you take a single medicine, and it works great, but it doesn't keep working after a while. So that's resistance, where the cancer kind of figures a way out. So is the idea if you combine medicines all at once that cancer can't develop that resistance?

Dr. Wierda:
Right. Or there [are] fewer cells that are potentially able to develop that resistance.

Andrew Schorr:
Okay. So you've been involved in research. They have, too but what we had called ABT-199, venetoclax, you and Dr. Seymour in particular. So there's been a lot of buzz about that. So how would that work in combination with ibrutinib (Imbruvica) or some of these other medicines that we have?

So your question was about how the two drugs may work. I think from Varsha's lab and also from Varshagani's lab and also from Metho David's lab, we've seen some results where they've combined different drugs and looked at the effects on cells in the test tube. And certainly one of the most promising signals to come up is the combination of a BCL receptor antagonist like ibrutinib and a Bcl-2 antagonist like venetoclax.

That in itself is very promising because the laboratories have told us that when you mix different drugs, that this is probably one of the most active combinations. Now, from my practical sense, these are two drugs, which are both taken by mouth as tablets, so they're convenient to give.

And as Dr. Wierda mentioned, they don't really have overlap in toxicity. So we can put them in a patient, and we won't get horrible overlapping side effects. Because one drug causes nausea, the other drug caused nausea, so you get very bad nausea. It's not like that. The toxicities are different. Lastly, when it comes back to your point about resistance, we don't understand why resistance happens. But we think that either the cells evolve under the pressure of treatment, or maybe amongst the many, many cells in our body it's based on the one or two cells that carry the resistant gene already. And if—suppress everything and allow those cells to grow up.

Andrew Schorr:
Stronger cells.

Dr. Tam:
Stronger cells. But if you think about it mathematically, it is highly unlikely for a cell in a given patient to be resistant to a potent drug like ibrutinib maybe one in 10 billion or something like that.

And if you find—put a second drug in, that one in however many billion cell also has to be resistant to the second drug. So the probability goes even lower and gets to a point where they're probably lower than the number of cells in a patient's body which are cancerous. And so it is possible that with combinations of two or three highly potent drugs, they will get to a stage where there will be more resistance. But only time will tell.