Sequencing Novel Agents for CLL

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Jeff Folloder:
What is the difference between a chemotherapy agent, an immunotherapy agent, and these novel inhibitors and small molecules?

Dr. Faber:
Absolutely, Jeff. To me, state-of-the-art is a perspective, and what we have are general chemotherapy agents like fludarabines (Fludara) and cyclophosphamide (Cytoxan) that you see there. When I used to teach med students and residents, we had an auditorium and how do our drugs work? I would say; imagine on the side doors that somebody came in with a hose and started spraying the room. A lot of you would get wet. Some of you are pretty quick, and you’d get behind the seat and you would stay dry. That’s kind of how our chemotherapy, like fludarabines and cyclophosphamide; it’s not very directive. It’s general, and so now instead of trying to affect the cell from a general aspect a blood cell is a sphere and it has proteins and there are antibodies like rituximab (Rituxan) and obinutuzumab (Gazyva), and it recognizes these proteins on the surface.

We had good success with the introduction of these monoclonal antibodies, and then as we learned more, when not everyone in a clinical trial responded the same way or in life; then we started to look inside the cell. Inside the cell we have a surface and we have another little sphere called a nucleus. There are pathways and the ways that cells communicate to live and die. Medicines like Ibrutinib and idelalisib (Zydelig) and venetoclax (Venclexa); the way that CLL cells have an advantage to grow after being signaled from the outside, these drugs address that and so to me, as I’ve said state-of-the-art is a perspective because we still have older therapies that work extremely well. We have newer agents that come to the front and then we learn more about further science that helps.

To me, there’s this ebb and tide of; we have traditional chemotherapy, we have immunotherapy, we have targeted therapy, we have novel agents depending on how you think of that, and really we restructure and juggle those so to speak. If you look on clinicaltrials.gov today you will see all versions of monoclonal antibodies and immunotherapies, and checkpoint inhibitors, so really as you circulate and find these combinations, to me that’s exciting because as everyone in the room here and online, it really can be individualized care. How do we sequence and how do we combine these agents to maybe be as good as FCR?

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