Where Are We Headed With Frontline CLL Treatment Approaches?

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

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

Andrew Schorr:
Okay. So, John, I know there are just some headlines from this conference, and you're a chair of one of the sessions. I know that there's data about ibrutinib (Imbruvica) having effectiveness for older patients earlier. And you talked earlier about moving drugs earlier. So is that where we're headed, now, with these new agents that have been approved for second line not just for older patients, and not just with certain subtypes of CLL but for a broader group we can use these pills earlier?

Dr. Gribben:
Sure. At this meeting, we've got the results of the RESONATE-2 trial, frontline treatment; ibrutinib versus chlorambucil (Leukeran). It's in the *New England Journal* this weekend. So right out there, outstandingly good results.

I think everybody knew that ibrutinib was probably going to be better than chlorambucil on the basis of how effective it was for very end stage patients. But I think the results are just outstanding. And it's very, very clear, now, that you are seeing better results the earlier you treat a patient. A big—slight but not let's say a big concern—a concern still remains if you use your best drug first, what does that leave you for later? I think in many respects that's also becoming a little bit of an old-fashioned idea.

Bill mentioned earlier we've seen trial after trial showing survival advantage for what we're doing by using our optimal therapy first. And probably I think this will become a treatment widely adopted I think even without licensing approval. At the moment, a lot of clinicians are using it.

We're certainly using it for patients who've got high-risk features at our presentation. There's been a big trial looked at watch and wait versus ibrutinib, which we haven't seen the results of, yet. But moving it forward seems to be a large component of what we're doing. What, of course, we also hope will happen is that it won't induce the kind of high-risk genetic features that the chemotherapy did. One caveat for all of these trials is that each one of those trials showing these new agents has been so much more success than the other agent. We've had a positive readout of the trial quite quickly—much more quickly than we've ever been used to with trials.

That's great for patients, because it got approval for these drugs very, very rapidly. But it does mean that when we're talking about long-term follow-up here, we're talking about one and two and three years on these trials. We really do need longer follow-up of these sorts of agents to really understand what impact alone they're going to have overall.

Andrew Schorr:
Okay. You mentioned about combinations. So the ideas can the drugs—we're moving some drugs up earlier as single agents, like ibrutinib maybe will be used for a lot more people right off the bat. Okay, so the ideas, though, he's saying what may happen two, three years. Are we shooting ourselves in the foot? We're getting great benefit now, but are we creating some other situations down the road? That would be the concern, right?

Dr. Tam:
It would be some concern, because we do know in the relapse setting that the rate of let's say ibrutinib related with mutations do rise after two years and beyond. On the flip side, with the frontline setting the response is simply more durable. There seems to be less cases of resistance being developed, albeit with shorter follow-up. So we can see the situation where when you treat the leukemia when it's not as genetically complex, that maybe you can get more durable control.

I guess the concern in a lot of our minds is actually the cumulative toxicity and cost of long-term treatment for these patients. Now we've moved to a point where probably the best treatments available are frontline now, and patients are living for a very long time in good health. Nevertheless, these drugs are not without side effects, as you pointed out. These drugs are very expensive. And what I meant was really now is how do we stop people from being on one of these drugs indefinitely, for the rest of their life, and how do we take the next step forward?

Which is why, as you mentioned before—and as Bill mentioned before and as John mentioned, cure I think is what we're aiming for. A limited duration of therapy—get rid of the last cell, stop the drugs.

Andrew Schorr:
Okay, I just want to summarize for a minute, and then I just want to ask about clinical trials. So what you're saying is there's a broader brush of patients, the wide group of patients now, you have medicines for them. Many of these medicines can be used earlier.

We still have monoclonal antibodies that have a place, right? So some people will still get some infused therapy, and there will be some people who still get some chemo. FCR still has a place for some people, I know, and certainly it's less costly than some of the other medicines, as well. But you're working on combinations that hopefully can get us to a point where you then can go off medicine. Maybe someday your immune system can take over. Did I get it right?

Group:
Absolutely.