Are We Closer to a CLL Treatment "Home Run"?

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Andrew Schorr:
Andrew Schorr on location at ASH talking about CLL with one of the guiding lights in it, Dr. Tom Kipps from the Moores Comprehensive Cancer Center at University of California San Diego, where I now live. This is going be my doctor in San Diego.

Dr. Kipps, we've talked many times, and news just keeps accelerating in CLL. So let's talk now about ibrutinib (Imbruvica) and the RESONATE 2 trial and what it might mean for people more broadly using that medicine. What do you think is going to happen?

Dr. Kipps:
Andrew, it's a very exciting time. As you mentioned, the RESONATE 2 trial was actually presented here at the ASH in 2015, and the paper just came out this week in the *New England Journal of Medicine*. And what the trial did was essentially to look at the use of ibrutinib, an oral agent, which is a, as you know, an inhibitor of BTK, and that compared to chlorambucil. So patients over age 65 who had some medical co-morbidities were actually randomized to receive either ibrutinib versus chlorambucil (Leukeran).

And I remember going over the results, and it was really quite striking. We anticipated that patients would tolerate ibrutinib well, and we'd have sustained progression-free survival provided they stayed on the medicine. But the patients treated with ibrutinib actually—actually fared much better than the patients treated with chlorambucil. In fact, they had a survival difference, which was quite striking.

We had appealed to the company Pharmacyclics to have a crossover design, so that meant that patients could start treatment with chlorambucil first. And if they were failing chlorambucil, they could switch over to the ibrutinib. Now, as you imagine, with the protocol requirements having to document progression there may be some delay in that switch-over, but we still were quite surprised to find a survival advantage.

So what does this mean? I mean, this is the use of ibrutinib as initial therapy. As you know, this drug has been approved by the FDA for treatment of patients who have failed or relapsed after chemotherapy and for patients with deletion in 17p who are noted not to be very responsive to chemotherapy. The question that now remains is whether ibrutinib should be considered as part of frontline therapy, and that's now being actively explored in other protocols, and I know that's going to be up for discussion by the FDA.

Andrew Schorr:
But there's a strong argument for it.

Dr. Kipps:
Well, I think so. I think we have to understand that chemotherapy has a place. Chemotherapy is effective. Chemotherapy, however, has gotten a very bad name, because it's the only tool that we've had, and it was used early and often and repeatedly so. And it's like anything. If you use a tool and you try to apply it for the wrong application, it actually can have some bad outcomes. So I think the connotation that chemotherapy is bad in any circumstance is actually maybe an overreaction in that chemotherapy potentially at the right applications may still have some role.

And I think we have to be very clear on what that role can be. I like to describe the chemotherapy as being like a surgeon's scalpel. If you put that in the hands of skilled surgeons, it can do some magic. If you put it in the hands of a 2-year-old, you're going to have some trouble. So I think with anything we have to be careful and mindful of the toxicities. We have to also look at the long-term follow-up data, and we have to really carefully analyze outcome data.

I'm also very excited about these nonchemotherapy approaches. You know me, from the very early days I've been trying to find alternative regimens other than chemotherapy. But I do think that for certain segments of the CLL population there could be some argument for this, particularly in younger patients potentially who have CLL cells that express mutated antibody genes. Some of the data outcome analysis from the CLL 8 study, from the German CLL study group and also from MD Anderson…

Andrew Schorr:
…look, had FCR 15 years ago, and I've had no treatment since then.

Andrew Schorr:
And so when you compare getting six months of therapy, which is, you know, hard to go through, but then you're done with it. If we can put this disease in the rearview mirror and not make it a day-to-day encounter that patients have to consider, I think that's an advantage. So I think that there's really a proper place for the appropriate use of chemotherapy.

But fortunately now it's not the only tool that physicians have. We know that chemotherapy, even though we have different chemotherapy drugs, they all work through a very common mechanism. And if you use that too often, then that mechanism gets broken, and the chemotherapy is not so effective on the leukemia. But it's still effective in the bone marrow killing off the normal cells that we need to survive.

Andrew Schorr:
Toxicity.

Dr. Kipps:
Yeah, the toxicity goes up, and the therapeutic index goes down.

Andrew Schorr:
All right. Let me ask you about this. Monoclonal antibodies, so Rituxan (rituximab), Gazyva (obinutuzumab), Arzerra (ofatumumab), all these monoclonal antibodies that are also used, somebody says, "Well, you've got these pills, Dr. Kipps, why are you saying I should have a targeted but infused therapy? Why do I have to be poked?"

Dr. Kipps:
Well, I think that it's clear that monoclonal antibodies have clearly provided a survival advantage for patients with CLL, and that's clear in earlier trials. One can ask the question, "Does that still apply to today?" I believe it does. We do know that with the work on these oral kinase inhibitors that we're not really getting home. Some patients describe it as being caught on third base, and they're worried about being tagged out trying to get home.

The monoclonal antibodies may enhance the degree of response. We're hopeful that we get more complete remissions and potentially even minimal residual disease, negative remissions. That is yet to be seen, but I think the monoclonal antibodies provide that edge, and they're also very specific for the tumor population.

We're very excited about the second- and third-generation anti-CD20s. The obinutuzumab is powerful. Some of our patients have described it as being like rituximab with an attitude. And it does pack a wallop. But if you get past the first initial infusion with the infusion reactions that we see, then patients tolerate it very well, and it can be very effective in clearing out the blood and the marrow of patients, more so perhaps than the drug rituximab.

Andrew Schorr:
Okay. There's also been news about another drug which had been ABT-199, venetoclax. What's the update on that and how it's going to fit in?

Dr. Kipps:
Well, I've been very excited about this category of drugs from the get-go, and in the early days we were doing work with a drug called gossypol, which is dried from cottonseed oil. And what this drug did was actually inhibited this protein called Bcl-2. We know that in CLL Bcl-2 is expressed at very high levels in CLL cells. And if you suppress Bcl-2, there's another protein that actually serves as an executioner called Bim. That's at very high levels. And it's like having a balance—like two Sumo wrestlers. And you put one out of commission, the other one falls over, and the leukemic cell dies very effectively.

So with gossypol, we were working on this. And then a drug came along called navitoclax, or ABT 263, that we worked with extensively. The old thinking was that you had to inhibit Bcl-2. Then it was discovered that there [are] various members of the Bcl-2 family. There's Bcl-X long, there's Mcl-1, Bfl-1. And so the new thinking was that you had to inhibit multiple Bcl-2 members.

But unfortunately when we did that with navitoclax, you inhibited not just Bcl-2 but other members of the Bcl-2 family. You inhibited a protein that also is important for the survival of platelets. And so the platelet survival went down. The platelet counts went down, not such a good thing. So the new thinking became you only have to inhibit Bcl-2, so we've come full circle.

I think with venetoclax, which is a very specific inhibitor of Bcl-2, we see very dramatic effects so much so that patients with very extensive tumor burdens have to be careful. When you start therapy, you can have such extensive tumor lysis that you get in trouble. You know, too much of a good thing can be a bad thing. And so patients have to be monitored very carefully because if the cells start lysing, then they release the contents of the cell into the body, you get very high levels of the intracellular contents into the blood.

Andrew Schorr:
Bad for kidneys.

Dr. Kipps:
Bad for kidneys. And also while it's not so bad for kidneys, but cells have a high level of potassium. We hear about potassium in fruits. We have very high levels of potassium inside cells. Potassium is very important in conduction. If you have too high a potassium level in the blood, guess what, your heart stops beating.

Andrew Schorr:
Oops.

Dr. Kipps:
And so the problem with tumor lysis syndrome was patients feel fine until their heart stops beating, so you have to follow carefully what's happening. Now, fortunately, it's only when you are starting therapy or when you ramp up therapy. We know now that that can be done safely by monitoring chemical tests during the early stages which patients are initiated on therapy.

There's also a step-wise regimen where patients take a small dose then a larger dose and a larger dose, and they're monitored with each incremental increase in dose. And I think once the patients get beyond that stage there's really no risk of tumor lysis occurring.

Andrew Schorr:
Okay.

Dr. Kipps:
So it's only when the change in dose, starting doses or increasing the dose. So patients—I have had patients now on ABT-199 or venetoclax now for years, and I've been following them, and they've been tolerating this drug very well. We've been monitoring the marrow biopsies, and some of our patients have actually gone into a very deep remission allowing us to even stop therapy. We were one of the first to stop therapy, because you know if you don't need treatment, it would be nice to know if you can stop and see if you can do without treatment. And some of these patients have done extremely well. They've been off therapy now longer than they were on therapy, and I think that this is very exciting.

Andrew Schorr:
I have to ask, Dr. Kipps, about the "C" word. I'm not talking about cancer, talking about cure. Tom, you've been at this a long time. You're seeing more medicines than ever before, and you have some patients with some medicines who have been able to stop therapy. Can some patients just go on with their life, and will you be able to say to them, Mr. Jones, Mrs. Smith, ostensibly I think you are cured?

Dr. Kipps:
Well, I think we're at a very exciting time, but we're also at a very critical time. Some people say CLL is done. We've got these new drugs, patients are living longer, patients are doing better, we should concentrate our efforts on other diseases. I think you can make these arguments, but I think that would be a mistake, because we've got the enemy on the run. And it would be best if we can follow up by chasing it down with further clinical trials, either sequencing these new therapies or giving them combination therapies, developing new treatments that can provide inhibition of other pathways that we're already inhibiting with these newer drugs, and hopefully we can actually then eradicate the disease entirely.

I think that's very feasible, and we should be putting our sights on that. I would suggest to CLL patients everywhere stay active, keep writing to your Congress people or what have you that, you know, CLL is here, but we can't be complacent. We have the enemy on the run. Let's go finish it off. And if we just rest our laurels right now, I'm afraid it's subscribing patients to very long-term courses of therapy which I'm of the opinion that there's no treatment on the planet that doesn't have side effects. Every treatment has side effects. We have to understand that, how to mitigate them. But if we can get patients through therapy and get them cured of the disease, that's as good as it gets.

Andrew Schorr:
Okay. Well, you've been working on it for so long, and you will continue. Dr. Tom Kipps from the Moores Cancer Center at the University of California San Diego, thank you for all you do.

Andrew Schorr on location at the ASH meeting in Orlando. Remember, knowledge can be the best medicine of all.

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