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ReachMD
www.reachmd.com
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(866) 423-7849

Discovering a Unique Target in CLL Treatment

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm your host, Dr. Charles Turck, and joining me to discuss a unique target in the treatment of chronic lymphocytic leukemia, or CLL for short, is Dr. Justin Taylor. Dr. Taylor is an Assistant Professor in the Division of Hematology, as well as a member of the Translational and Clinical Oncology Program at the Sylvester Comprehensive Cancer Center of the University of Miami Miller School of Medicine. Dr. Taylor, thanks for being here today.

Dr. Taylor:
Thank you for having me.

Dr. Turck:
So let's start with some background on anti-apoptotic Bcl-2 proteins. Dr. Taylor, would you tell us a little bit more about their roles in human physiology?

Dr. Taylor:
Sure. So Bcl-2 proteins is a family of proteins of which there are many, but Bcl-2 was the founding member and the one we're going to talk about today. So its full name is B-cell lymphoma 2 because it was found in a B-cell lymphoma called follicular lymphoma, where it's involved in a translocation, which is associated with causing follicular lymphoma. But we know that it's also involved in other types of lymphoma, like CLL, as well as other blood cancers and even non-blood cancer solid tumors.

And so what Bcl-2 does is it's an anti-apoptotic protein. It opposes apoptosis, and it does this by binding to and sequestering BH3-only peptides. So these BH3-only peptides, their normal role is to activate the pro-apoptotic proteins, Bax and Bak, and cause the cascade of apoptosis through the mitochondrial membrane of cytochrome c release and reactive oxygen species. When you have Bcl-2 around it sequesters the BH3-only peptides by binding to them and not allowing them to interact with Bax and Bak, and then it prevents apoptosis, also known as programmed cell death. So in the cancer setting when these cancer cells are staying alive longer than they're supposed to, they're not undergoing programmed cell death Bcl-2 is playing a big role in that by this mechanism of action.

Dr. Turck:
And I was wondering if you could elaborate a little bit more about the role that Bcl-2 proteins play in the pathophysiology of CLL.

Dr. Taylor:
Sure. So in CLL we do not see that translocation that involves Bcl-2. However, Bcl-2 is upregulated through other mechanisms, and we believe that nearly all of CLL has some form of Bcl-2 upregulation. For example, in CLL with deletion of 13q, chromosome 13q that deletion causes the micro-RNA in that region to be deleted or be gone. Those micro-RNA normally play a role in regulating Bcl-2, causing its expression to be lower. So when you lose that regulation through micro-RNA loss in deletion 13q then Bcl-2 can be overexpressed. In CLL that does not have 13q deletion, it can be overexpressed through amplification or epigenetic mechanisms so that we think that Bcl-2 is involved in the pathophysiology of CLL.

Dr. Turck:
So then what happens at the macro level, or clinically, if Bcl-2 proteins continue in a dysregulated state?

Dr. Taylor:
Yeah, so again, that's keeping the cells alive, as well as just in the baseline status of CLL. However, when you apply therapies, such as, we used to use chemotherapy Bcl-2, can also play a role in the resistance to the cell death related to those chemotherapies. Nowadays,

we use more targeted agents like BTK, or Bruton's tyrosine kinase inhibitors. And Bcl-2 can also play a role in opposing the cell death related to BTK inhibitors. So not only does it play a role in the pathophysiology, but it can also be involved in treatment resistance, and even transformation to Richter syndrome, which is the end outcome of untreated CLL. Not all patients, but some patients, the CLL actually transforms into a large B-cell lymphoma called Richter's transformation, and Bcl-2 can play a role in that as well. So it's involved all throughout the different stages of CLL.

Dr. Turck:
For those just tuning in, you're listening to Project Oncology on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Justin Taylor about the role of anti-apoptotic Bcl-2 proteins in chronic lymphocytic leukemia, or CLL.

Now given everything we've discussed so far, Dr. Taylor, I'd like to dive into some potential solutions and treatment options. So you started to get into some of this before, but would you tell us about how we can regulate or modulate the actions of Bcl-2 proteins in our patients with CLL?

Dr. Taylor:
Yes. So the Bcl-2 inhibitors, as they're called, is a major class of therapies that have been approved for CLL. And so these are called inhibitors, but unlike kinase inhibitors, like BTK inhibitors, there's not an enzymatic function that they're inhibiting. Rather, they are binding to Bcl-2, where the BH3-only peptides bind. So they're also referred to as BH3 mimetics because they mimic the BH3-only peptides, and they bind to Bcl-2, where Bcl-2 normally sequesters the BH3-only peptides. This frees the BH3-only peptides to interact with Bax and Bak and trigger the apoptotic cascade as I mentioned before, is part of the programmed cell death of cells, and thus, using these Bcl-2 inhibitors we're able to cause the CLL cells to die.

Dr. Turck:
And what kind of impact does targeted inhibition have on the overall treatment of CLL and related patient outcomes?

Dr. Taylor:
Yeah, so Bcl-2 inhibitors like venetoclax, is approved for the use in CLL. It's given now in combination with the anti-CD20 antibody, obinutuzumab. But it was first tried as a monotherapy, and it has also been tried with other anti-CD20 antibodies like rituximab. And it has effect as a monotherapy by itself. And actually, when it was first developed, it had such a dramatic effect, it caused something called tumor lysis syndrome, where all the cells are dying again from this induction of apoptosis. And when they die, they release some of the intracellular chemicals that can affect the kidneys. And so this is called tumor lysis syndrome and that was a big side effect, basically, of the Bcl-2 inhibitors when they were first being developed. Luckily, we recognize that a ramp-up schedule has been in place and in combination with other agents like the approved combination of venetoclax with obinutuzumab that's now seen much less, and it's something that's carefully monitored for and controlled again, with these ramp-up protocols in place. So they are very effective, and it is a standard treatment option for frontline CLL treatment, especially in older individuals, and then in the relapse setting, it can also be used. Again, it's been studied there with other combinations.

We're beginning to look at combining Bcl-2 inhibitors with BTK inhibitors, but that's not yet approved in the U.S. It has been approved in Europe, with ibrutinib being the BTK inhibitor and venetoclax being the Bcl-2 inhibitor. But that's still under investigation in the United States. But I would just say that you know that from the trials that we've seen very promising effects of combining Bcl-2 inhibitors with other inhibitors, like BTK inhibitors, so we'd expect that to be looked at by the FDA, and maybe seeing an approval here sometime in the future.

Dr. Turck:
Well, speaking of that, are there any studies or research on the horizon for targeting Bcl-2 proteins in CLL that you find particularly compelling or exciting?

Dr. Taylor:
Yeah, so there are a couple of new Bcl-2 inhibitors. So as I mentioned, venetoclax was the first-in-class Bcl-2 inhibitor, and very effective, approved for CLL and being now used in different combinations. There are some new Bcl-2 inhibitors that work with the same mechanism of action, but maybe more potent. It still remains to be seen. They're still undergoing clinical studies. They're not yet approved, but they're trying to improve upon venetoclax to become even more potent Bcl-2 inhibitors.

And the other trials that I'm excited about in this space is currently we don't know what is the best treatment option for patients with CLL as a frontline treatment. You have many options. You have BTK inhibitors, of which we now have three different ones approved in the frontline: ibrutinib, acalabrutinib, and zanubrutinib. Zanubrutinib and acalabrutinib have less side effects than ibrutinib and have been shown in studies to have equal efficacy, if not better efficacy. So those are the frontline BTK inhibitors that are commonly being used these days. But you also have the option to use venetoclax with obinutuzumab, and it's not really known what's the best one to start

with; often it has to do with the patient's preference. The BTK inhibitors are pills that can be taken. You don't need a ramp-up, and you don't have to get any other treatment with it. With venetoclax, again, it also is a pill, but you have to do the ramp-up, as well as it's approved in combination with obinutuzumab, that's an anti-CD20 antibody, so you have the patients have to come in to get that as an injection. So it could just be the patient's preference.

The preferable thing about the combination of venetoclax with obinutuzumab is it's a time-limited therapy, as opposed to BTK inhibitors, which are taken for continuously. The venetoclax/obinutuzumab does not have to be taken continuously. And right now, the CLL17 study from the German CLL study group is doing a phase 3 randomized trial to look at ibrutinib monotherapy, again, maybe not our best first choice BTK inhibitor these days, but a BTK inhibitor nonetheless comparing that with the fixed-duration venetoclax plus Obinutuzumab, as well as a third arm where they're combining the fixed-duration ibrutinib plus venetoclax.

Dr. Turck:
That's a great look ahead as we come to the end of today's program. And I'd like to thank my guest, Dr. Justin Taylor, for joining me to discuss the role of Bcl-2 proteins in targeted inhibition in the treatment of CLL. Dr. Taylor, it was great having you on the program.

Dr. Taylor:
Thank you. Great to be with you.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit Project Oncology on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.