Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/tackling-adverse-events-associated-with-disruption-of-b-cell-receptor-signaling-a-multispecialty-approach/13796/

Released: 06/30/2022
Valid until: 06/30/2023
Time needed to complete: 15 minutes

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

Tackling Adverse Events Associated with Disruption of B-Cell Receptor Signaling: *A Multispecialty Approach*

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Tackling Adverse Events Associated with Disruption of B-Cell Receptor Signaling: *A Multispecialty Approach*" is provided by Prova Education.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Flinn:
This is CME on ReachMD, and I'm Dr. Ian Flinn. Today, Dr. William Wierda and I will be discussing adverse events associated with the use of BTK and BCL-2 inhibitors in patients with chronic lymphocytic leukemia, or CLL, and how to best prevent or manage them. We will also briefly touch upon the addition of an anti-CD20 monoclonal antibody and how this can affect patient outcomes.

Dr. Wierda, welcome to the show.

Dr. Weirda:
Thank you, Ian. Happy to be here.

Dr. Flinn:
So let's dive right in. Bill, what are the most significant adverse events associated with ibrutinib therapy in the treatment of CLL?

Dr. Wierda:
So, we've had ibrutinib now for many years and there have been a number of clinical trials evaluating ibrutinib and the activity of ibrutinib, and we have a much better idea about the side-effect profile and toxicities associated with ibrutinib. As an agent, in and of itself, and also in comparison to other drugs that fall into the category of irreversible inhibitors of BTK, it inhibits BTK irreversibly. There are other kinases that are inhibited, and this, we think, is one aspect that weighs into the side-effect and toxicity profile of ibrutinib. We talk about toxicities, and your question was, "What are the most notable or severe adverse events?" So, let's talk a little bit about both of them, though we'll start with the most, potentially severe, or important side effects that we see with ibrutinib. Those are uncommon. I will say that they're occurring in probably about less than 5% of patients. The one main one that we worry about is atrial fibrillation. The longer patients are on ibrutinib, the more likely we may see this adverse event emerge. And I think we'll talk about the head-to-head comparisons with other irreversible inhibitors of BTK. But atrial fibrillation and cardiac arrhythmias is one of the major, significant, notable side effects that we focus on. It does inhibit platelet function, so it does also have anticoagulating properties, as do other BTK inhibitors. They can be manifested by increased bleeding, bruising. A more notable or severe side effect may be significant bleeding events with ibrutinib. Those are uncommon also; they happen in less than 10% of the patients. And then, hypertension, we see as a side effect that can be notable. This can emerge as patients remain on treatment long-term and is usually managed with antihypertensives. So there are other, minor toxicities that occur in a fair number or percentage of patients. Those can be GI intolerance, diarrhea, constipation, etc. Those are uncommon as severe events, grade 3 or greater, but are relatively common as low-grade events, and they happen in perhaps about 50% of patients. Fatigue can be seen, but again, low grade, less than grade 3. Arthralgias, myalgias—also low grade,

but can be seen in about a quarter of the patients. Those are the major side effects that we see with ibrutinib.

Dr. Flinn:
So, I agree with you, Bill and I remember when this drug was first developed. I really thought that this was one fantastic, paradigm-changing drug, that really wasn't associated with any adverse events. But as it moved earlier in the natural history of the disease, I think that's really when we began to appreciate some of these adverse events that we didn't really realize in the patients who are refractory to chemoimmunotherapy—and they were incredibly sick at that time—so, I think that's really opened our awareness, the earlier the use of this drug in CLL.

Dr. Wierda:
Yeah, and I will reflect with you, also, that in the beginning we didn't really see these cardiac events very commonly, and it wasn't until we had the drug available for several years that we were saying, "Oh, we're starting to notice, perhaps, atrial fibrillation–associated or cardiac arrhythmias." So, Ian, maybe you can touch, also on acalabrutinib and how that may be distinguished from ibrutinib.

Dr. Flinn:
Acalabrutinib is FDA-approved for the treatment of chronic lymphocytic leukemia. And the hypothesis behind the development of acalabrutinib is that perhaps using an inhibitor that was more specific for BTK, that didn't hit some of these off-target kinases, that you might have an equal or better efficacy without, perhaps, some of the adverse events that we see with ibrutinib. And so now we see that perhaps there are less of the adverse events that you just mentioned. Perhaps they still exist, but just to a lesser degree, and that was from single-arm trials. That certainly seemed to be the case. But now we have a randomized trial in ELEVATE-RR, or ELEVATE Relapsed Refractory, which is a study that compared, directly, acalabrutinib to ibrutinib in patients with relapsed chronic lymphocytic leukemia. And this study is really quite important because it eliminates some of the differences. And so there were certainly less cardiac events, less atrial fibrillation, less of the hypertension that you mentioned, that was seen as patients stay on ibrutinib. There were less major bleeding events, and all these events were seen to be significantly improved. And some of these, selected, other, perhaps not as important as cardiovascular events, but there is also less diarrhea, less of the arthralgias, which just can be really difficult for patients, especially in the frontline setting, and a variety of other minor adverse events as seen with ibrutinib. There were some unique increases, right? Headache was a fairly prominent event that occurs with acalabrutinib. Thankfully, it generally only occurs in the first month of therapy, and it's generally grade 1-2. And finally, for reasons that aren't clear to me, there's a little bit of increase in cough. In fact, there's cough with both ibrutinib and with acalabrutinib, but a little bit more with acalabrutinib. Bill, what is your perspective on this?

Dr. Wierda:
I agree with everything you said. I think one of the things that I would point out also, recently, there was an update of the prescribing information for ibrutinib, with recommendations for dose reduction, which is new. And that's based on data that they had assembled. Dose reduction for cardiac events for ibrutinib, which usually we think about switching drug when patients have these types of events, but now there is some recommendation for dose reduction for ibrutinib, which we didn't have previously.

Dr. Flinn:
Yeah, that's an important point.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Ian Flinn, and here with me today is Dr. William Wierda. We're reviewing toxicities associated with BTK and Bcl-2 inhibitor therapy in CLL, as well as approaches to prevent or manage adverse events to keep our patients on therapy.

So we've looked at the 2 major BTK inhibitors. So let's now turn to the BCL-2 inhibitor, venetoclax. Bill, what adverse events are we seeing with that agent?

Dr. Wierda:
I've had the pleasure of being able to work with venetoclax through the phase 1 clinical trial. I think you also were involved in the early studies with venetoclax, and with that experience, we learned of a couple of toxicities that are notable for venetoclax.

Venetoclax, as you mentioned, is the inhibitor of BCL-2. It blocks BCL-2 and favors apoptosis, particularly in CLL cells. They're exquisitely sensitive to venetoclax and induction of apoptosis. So what we saw early on in the clinical trial—the phase 1 clinical trial—were cases of patients who had overwhelming tumor lysis syndrome, because of rapid death of a large number of leukemia cells. And in those early clinical trials, we developed a system of evaluating patients for their risk of tumor lysis syndrome, and there is a prescribed initiation and ramp-up algorithm based on risk for tumor lysis syndrome. If we follow those recommendations, tumor lysis syndrome with venetoclax is extremely uncommon. The other side effect that we see, that can be an issue, is cytopenias, particularly neutropenia. That can occur early on after their ramp-up when they have a fair amount of disease in their marrow still, and the normal cells that are there may be having some challenge with generating adequate numbers of neutrophils, etc. So, I'll be very generous about using growth

factor early on if patients have neutropenia, grade 3 or 4 neutropenia in the first 6 months or so of initiation of venetoclax, working towards having an effective dose so they can clear their marrow out. If it's past the first 6 months, we also see neutropenia. That's more directly effect of the drug, and in those cases, I will commonly reduce the dose of the drug to manage the neutropenia. And then less commonly, and less severe, we see GI intolerance with venetoclax, sometimes nausea, diarrhea. A couple things that can be done for that: one is dose reduction, two is sometimes I'll tell patients to take their dose in the evening, so that they don't have to deal with the GI stuff while they're sleeping.

Dr. Flinn:
Thanks, those are important points. I guess one thing to add is just to monitor the renal function. Clearly, those patients who have some renal insufficiency to begin with, it might be a more challenging drug to use in that setting.

Dr. Wierda:
And that ties into the risk of tumor lysis, and, you know, some of the things that we do aggressively; hydrate patients, particularly those with renal insufficiency. We talked a lot about side effects that can be seen. We touched a little bit on some of the methods to manage those side effects. Maybe, Ian, you can elaborate a little bit more on what your practice has been, and recommendations for management of toxicities and side effects associated with the BTK and BCL-2 inhibitors.

Dr. Flinn:
Yeah, sort of a large gamut of issues there. I think for the BTK inhibitor, there are a couple things. One is some of the nagging sort of issues that occur to people, such as the arthralgias, especially with ibrutinib, and for that, it's not easy. I mean, I think, perhaps stopping the drug, waiting for the arthralgias to get better, restarting, perhaps at a lower dose. Occasionally, we have had to use steroids in that setting, and that can help as well. But these days, I think you have options in BTK inhibitors, and so if something like that type of issue comes up, then it's also possible just to change to another BTK inhibitor. We know from a series of studies that show that by switching from, say ibrutinib to acalabrutinib, then a lot of times that the adverse event doesn't occur. The bigger issue, I think is atrial fibrillation, and that's a big thing to handle. And, in the beginning we thought if this is the only drug for the patient, you got to keep them on, you got to manage through. And I think you can manage through, for many patients. That might be…but you have to be careful about the anticoagulation. You have to be careful about the antiarrhythmics, and perhaps the dose. And so, I would avoid, if you keep a patient on ibrutinib, or one of the other agents, you just need to be cognizant of these, and be aware of the bleeding risk. For some patients that just absolutely have to stay on that medication, and you need to anticoagulate them, and they are in atrial fibrillation…I even had to put a Watchman in patients. And so, to be able to get them off anticoagulation, that's clearly a rare approach, but that can be done. I would avoid warfarin, indeed, and perhaps use the direct inhibitors if you're using a BTK inhibitor. I think you've hit a lot of the strategies for BCL-2 inhibitors in management of TLS. One thing that we probably didn't talk about, though, is you can often avoid TLS and the need for as much of the monitoring. For instance, someone who has very high risk for tumor lysis syndrome, you can debulk them using the monoclonal antibody obinutuzumab. And that can put them into a lower risk category for tumor lysis syndrome. Bill, what have I left out?

Dr. Wierda:
Yeah, so maybe a couple of thoughts along the lines of the bleeding issue, with the irreversible inhibitors of BTK. I think it's important to just remind people that if patients have minor surgery, we recommend stopping 3 days before and 3 days after. Major surgery, it's a week before and a week after. As you mentioned, we do worry about the patients who are on more than one anticoagulant. My rule of thumb is usually to have them on a BTK inhibitor plus only one other agent. So, not a platelet agent, aspirin, and a BTK inhibitor. The other topic, maybe, that we didn't really touch on was the proton pump inhibitor avoidance for acalabrutinib because of the effects on drug absorption. Hopefully, that will go away soon, with the new formulation of acalabrutinib. And perhaps, with regard to the CD20 antibodies, just reminding people that we do see tumor lysis syndrome with the CD20 antibodies, so you kind of have to be careful and make sure patients are well hydrated, and monitor them some for tumor lysis, particularly if they're previously untreated and you're just starting them on a CD20 antibody. With obinutuzumab, we also manage the infusion-related reactions, which are typically occurring on the first dose. And as you know, we split the first dose to 100 and then 900 on day 2, to mitigate and manage the infusion-related reactions.

Dr. Flinn:
Great, great. I guess that my experience is it almost doesn't matter how much of the CD20 you get in that first day. So you mentioned the split dosing, we use it with obinutuzumab. We often use split dosing with rituximab. But my experience is just getting some CD20 into someone on that first day, and then next day it's much, much easier to give that.

Well, this certainly has been a fascinating conversation, but before we wrap up, Bill, do you have one take-home message that you want to share with our audience?

Dr. Wierda:

I think maybe one take-home message is that these agents, these small molecule inhibitors, whether we're talking about BTK or BCL-2 inhibition, are extremely effective. They have unique side effects and toxicity profile. We expect to have a reversible inhibitor relatively soon. That drug also will have its unique side-effect and toxicity profile. So as long as we know what we're dealing with, we can easily manage through them, and again, they're really treatments that have fundamentally changed how we manage patients with CLL.

Dr. Flinn:
Yeah, I think you couldn't have said it better. I think these are major advances in our treatment of CLL. We have a number of different choices. The vast majority of patients do really, really well on these therapies, and within the BTK inhibitor class, we have a choice of different therapies, and so, you know, I wouldn't be afraid to switch from one therapy to the next, rather than giving up on that class.

Dr. Flinn:
Unfortunately, that's all the time we have today. So I want to thank our audience for listening, and thank you, Dr. William Wierda, for joining me and for sharing all your valuable insights. It was great speaking with you today.

Dr. Wierda:
Thank you, Ian. It's been a pleasure speaking with you today and sharing our thoughts on small molecule inhibitors and side effects.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Prova Education.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Prova. Thank you for listening.