ASH 2017: Dr. Jennifer Brown on Bleeding Problems with Ibrutinib in CLL - Transcript

Dr. Brian Koffman – Hi. I'm Dr. Brian Koffman. I'm a family doctor and a CLL patient, myself. I'm here on the last day of ASH 2017 in Atlanta, Georgia, as the Medical Director of the CLL Society.

Dr. Jennifer Brown – And I'm Jennifer Brown. I'm director of the CLL Center at Dana-Farber Cancer Institute and Associate Professor of Medicine at Harvard Medical School.

BK – Dr. Brown, ibrutinib has changed the way we treat CLL, but there's been some rare, but very serious bleeding problems with it. You've done some research on this. Can you share what you've found and presented here at ASH?

JB – I've had the opportunity to actually look across four of the registrational trials, in collaboration with Pharmacyclics and Janssen, at the events on those trials, as well as including additional single-arm studies with ibrutinib, so there are multiple different populations that we've looked at.

BK – So, a big, broad area of patients?

JB – Exactly.

BK – Looking at everybody who had a bleed, essentially.

JB – Actually, we're looking at everybody comparatively, between the arm that got ibrutinib and the arm that didn't.

BK – Oh, okay.

JB – So, the randomization helps with what we're able to look at. And it did include three trials with CLL and one trial with Mantle Cell Lymphoma. And the rate of major hemorrhage was about 3% in the CLL patients, which is consistent with what we were expecting. And interestingly, if you do an exposure adjustment for the duration of time people are on ibrutinib, compared to the shorter duration of time they're on comparator, the risk ends up being about the same per unit time on the agent.

BK – So, let me stop you there. So, what you're saying there is, because you take ibrutinib continuously, and people may be on it for a year, or two years, or longer, where the comparator is often chemo or immunotherapy, where often the patient is on it for six months, or even less, so… but you're still looking at it over that same period of time, so if you just looked at the ibrutinib for the six-month to six-month, then the numbers were more similar.

JB – That's right. Exactly. But there's an ongoing risk over time on ibrutinib. Now, one factor though, although there were many types of hemorrhages that were balanced, the brain hemorrhages, as well as the fatal hemorrhages, were exclusively in the ibrutinib arm, although there were very few, less than 10.

BK – Less than 10, out of how many patients?

JB – 750.

BK – Okay. And do we know what risks put somebody for one of these? Beause these are catastrophic, I mean, obviously death, but a brain hemorrhage is catastrophic. So, is there ways that you as a clinician could say, "Hey, maybe not ibrutinib for you", or, "You're at high risk", or is there things that tell you when you're having that conversation with the patient?

JB – So, absolutely. We haven't been able to look formally at -risk factors for those catastrophic events, because there are just too few, even in this large dataset. But when I think about it with a patient, I look at what other medications they're on for example, if they require ongoing anticoagulation, blood thinning, or even

anti-platelet agents like aspirin, although the latter is pretty safe, and I can comment in a minute on what we found about that for the general population. But that is one factor that I certainly consider. If a patient has had a history of any major bleeding, or any brain bleeding, particularly that was very serious, that would certainly give me pause, particularly if it was due to something that is not easily fixed. You know, if it's due to an ulcer that can be healed or removed, and is no longer present, then that's one thing. But if it's due to an ongoing potential problem, that would definitely give me pause. Overall, I feel that as we've gained experience with ibrutinib, the bleeding issues are something that we've learned how to manage much better. In the beginning, I was very hesitant to use any full-anticoagulation (blood thinning) with patients on ibrutinib, but increasingly, especially for the patients who develop atrial fibrillation (heart-rhythm problem) we are using, typically, apixaban, which has the best safety record from the cardiology literature, and we've done fairly well with that. However, in this…

BK – So, I'm just going to stop there, too, because what's evolved too, while ibrutinib has evolved, also the medications that we use to thin the blood in people that are high-risk for a blood clot have evolved dramatically over the last 10 years. So, it used to be just warfarin (the blood thinner) and heparin (which is an injectable), now we have much more medications that have a different therapeutic index, a different safety profile.

JB – Exactly. And although there were limited numbers of patients on each of these individual agents in this analysis that I've reported here, there were some, and it was clear that the risk of a bleed was higher in the patients receiving the warfarin, and it was actually also a little higher in the heparin patients. The lowest was actually with the novel oral anticoagulants, of which apixaban is one. And so, the numbers were small, that was somewhat reassuring. And in the overall analysis, when we looked at what the risk factors were for a bleed, having Mantle Cell Lymphoma, compared to CLL, was actually one of the risks. The baseline rate was higher in that disease.

BK – Could that be the dosing, because, don't you dose at a higher rate for Mantle Cell?

JB – It is dosed higher, so that's formally possible, we don't know.

BK – Okay.

JB – But Mantle Cell Lymphoma also commonly involves the GI tract, for example, and we do know that sometimes we see the bleeding…

BK – Right.

JB – … from the GI tract. The other issue was that some of the patients with Mantle Cell Lymphoma seem to have lower platelet counts early on, and then got chemo-immunotherapy, so that may also have worked together to promote the bleeding with Mantle Cell. And then the other primary risk factor was being on one of these blood thinners or an anti-platelet agent. Ibrutinib didn't actually turn out as a risk factor in this multi-variable analysis for the major hemorrhages.

BK – Wow. So, I think things like hypertension, or elderly, or none of these things would have been risk factors, is what I'm hearing from you?

JB – Right, and…

BK – So, what's the take-away message for a patient here in terms of whether they should be concerned about a bleeding problem, if they're going to see their community hematologist, that ibrutinib is an appropriate choice for them? Maybe they've had some coronary disease, or some on anti-platelet drugs, what advice would you give them? What discussion should they have with their hematologist about this?

JB – Right. I would say it's still very much the same as it was before these data, which is that, aspirin I view as basically okay, although in my experience, occasionally, people will have very severe bruising with it, and need to come off, but aspirin, not really a problem. The clopidogrel class of anti-platelet agents, however, we had very limited experience in this dataset, which also looked like there were a higher rate of bleeding, and so I continue to be very, very cautious, and try if at all possible to avoid that class of agent if the patient's going on ibrutinib. And if someone requires anticoagulation, I tend to favor switching to one of these novel oral anticoagulants. And apixaban comes with a lower dose, which we often use as well, to decrease the risk. And then things like fish oil and vitamin E, that were excluded on the clinical trials, I usually advise people not to take if they have been. And then, one of the most important things is to hold ibrutinib for three to seven days before any major procedure, and after any major procedure. Because in the clinical trials, many of the significant bleeds were around the time of procedures.

BK – Dr. Brown, thanks so much. Thank you.