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How Do We Make Sense of Guidelines and Apply to Our Everyday Practice?

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Dr. Connors:
Hello, and welcome to our roundtable discussion on Aspects of Cancer-Associated Thrombosis, Both the Treatment, Management, and Prevention. I'm Dr. Jean Connors, a Hematologist at Brigham and Women's Hospital and Dana Farber Cancer Institute in Boston, Massachusetts. And with me today, I have two outstanding colleagues.

Dr. Ay:
Yeah, hello, my name is Cihan Ay. I am from the Medical University of Vienna. And it's a pleasure to be with you today.

Dr. Khorana:
Hi, I'm Alok Khorana. I'm a Medical Oncologist at the Cleveland Clinic in Cleveland, Ohio. And likewise excited to be here today.

Dr. Connors:
Yes, and so we, you know, I think we can all agree that we've seen marked improvements in care and in significant attention paid to the management of thrombosis in patients with cancer. Certainly in the last decade, we've had improvements in treatments that make life easier for our patients. And we've had improvement in sort of identifying risks, and balancing risks and benefits. With that, we - guidelines have been developed the address management and treatment of cancer-associated VTE.

And I wonder, Alok, if you could just briefly comment on these guidelines and how you view the role of these guidelines in your daily practice.

Dr. Khorana:
Yeah, we've seen some major changes in the treatment guidelines for cancer-associated VTE in the past several years, from going, you know, if we go back two decades, it was just vitamin K antagonists alone. And then for the last decade and a half, it was sort of a one-size-fits-all approach that every cancer patient with VTE should get 6 months of low-molecular-weight heparin monotherapy.

But in the latest version of the guidelines, we see a great deal more individual ability to individualize treatment, direct oral anticoagulants, such as edoxaban or rivaroxaban, apixaban for many patients, low-molecular-weight heparin monotherapy for other patients for whom bleeding, particularly GI bleeding, is a concern, or a mix and match of these approaches. So I think there's a greater emphasis on individualization and understanding both the risk of recurrent VTE, and the risk of bleeding in the latest iteration of the guidelines.

Dr. Connors:
Yeah. No. I think there are vast improvements, as many patients who've been on anticoagulation, even with cancer for a number of years, would say.

But Cihan, I wonder, when you look at your daily practice and the types of patients represented in your practice, whether they be inpatient or outpatient, do the guidelines help with your approach to managing these patients?

Dr. Ay:
I think it's very good to have these guidelines. Because in the guidelines, the basis for the guidelines is that the latest evidence is extracted from the literature and it's evaluated. And then you get a good synthesis not only of the evidence, but also suggestions for how to treat in specific clinical situations. For instance, so in guidelines, they focus on the different clinical scenarios that we see in our clinical practice. So for instance, a cancer patient that is hospitalized and for major cancer surgery, so how to perform thromboprophylaxis after major cancer surgery. So there is a clear statement here what to do then. There are statements on other

patients who are hospitalized for medical illness or other reasons.

And then they also really specify how to treat a patient with a cancer, based on the on the trial data that we had. And we had a couple of trials in the last year. So we didn't have the chance because of the pandemic to discuss probably those trials in detail that compared DOACs with low-molecular-weight heparin, which was the gold standard, as Alok mentioned, for one and a half decades.

Dr. Connors:
Yeah. No. I think very exciting times just within the last 5 years with regard to the cancer-associated thrombosis. And, you know, we had a - DOACs had emerged on the scene for treatment of VTE in the non-cancer population, in 2012-2014 even for some of them, and many of us may have been using them, if you will, off-label, to treat cancer-associated VTE in patients that we hoped we were selecting that would benefit compared to low-molecular-weight heparin. But it is very nice to see Hokusai VTE cancer, the SELECT-D trial, and certainly CARAVAGGIO, which I was part of which was presented March 2020 at ACC.

So again, I think it's good. And I think we've all - all three of us have been involved in writing guidelines for different societies. And I think - I don't know, Alok, if you can confirm that - I believe all societies that have written guidelines as far as I'm aware, whether it's in ESMO, ASCO, ISTH, I believe, ASH as well, And societies I'm probably missing, now list DOAC as first-line for treatment. I don't know if you want to comment on that and how they might differ or be similar, particularly with regard to where low-molecular-weight heparin ranks on their recommendations for treatment of cancer-associated VTE.

Dr. Khorana:
Yes, that's absolutely correct that all of the guidelines have responded to the data from randomized clinical trials. And, you know, I think it's wonderful that all of these different trials were specifically conducted in people with cancer rather than extrapolating data from non-cancer populations into cancer. Because cancer

patients are at higher risk for recurrent VTE and are at higher risk for bleeding than the non-cancer population. So I think it's fantastic that these trials were done in a specific cancer population.

And the guidelines have generally been very much in agreement adding direct oral anticoagulants to first-line management of cancer-associated with VTE. If people are in the hospital, you might want to start off with a parenteral drug such as heparin. If people are in the outpatient setting, we now have options to start patients directly on direct oral anticoagulant, hopefully avoiding the need for urgent care visits or emergency room visits or even a brief hospitalization.

And in general, the guidelines are in accord across these different societies saying that yes, for most patients, direct oral anticoagulants are an option. And the real caution where they interject is in people with GI bleeding and risk of GI bleeding where they're saying, well maybe consider a low-molecular-weight heparin, but even here, there's flexibility and the ability to take patient preferences and values into account before making a clinical decision.

Dr. Ay:
And another area where the guidelines are also in agreement is the setting of primary prevention in the outpatient setting in cancer patients receiving systemic anticancer therapy. So we had, over the last years, two randomized controlled trials, where primary thromboprophylaxis with a DOAC was done based on risk assessment. So patients at high risk of VTE were randomized to a DOAC versus placebo. And here a risk assessment model was used that has been developed many years ago, 2008, published by Dr. Alok Khorana and colleagues. That was the basis for these trials. And here, it's also wonderful to see that the guidelines say, 'Look, we have evidence, primary - it's time for primary prevention based on risk assessment,' but I see here in clinical practice while in treatment, so we implement guidelines. But in the prophylaxis setting, I don't see at least in the setting where I work a systemic implementation of the guideline recommendation with regard to primary prevention here.

Dr. Connors:

Yeah, before – Alok, before you get to comment on your excellent work there, I will echo what Cihan just said in that it seems that, like we as coagulation experts, and you Alok, as both a medical oncologist and coagulation expert, we're very, very aware of this data. I am very impressed that by using the Khorana Score to select patients at higher risk, you actually improve the risk benefit ratio, and you decrease the number needed to treat compared to the unselected patients in the trials with low-molecular-weight heparin, where the overall VTE risk was 4%, 5% in, you know, the placebo arm, a very hard sell. So your new data certainly is compelling. But to Cihan's point, implementing that, and the uptake has actually been surprisingly slow, I think in the oncology world. So I wonder, Alok, if you can comment on ways we might address that and improve on that.

Dr. Khorana:
Yeah, and I think that's a very important point that both of you have made, which is that, you know, it's one set of science revolves around developing concepts for clinical trials, conducting the clinical trials, demonstrating sort of the proof of the concept. A second and third is to make sure that the guidelines assess these trials fairly and provide a consensus. And both those things have happened. But there is a large part of science, implementation science, that needs to take into account and does take into account some of these developments, and that looks at ways of how can we implement this.

You know, just as a reminder, colonoscopy recommendations have been around now for 20-30 years, and yet, you know, 60% of the U.S. population doesn't get - only 60% of the U.S. population gets a colonoscopy. And that's after 20 years of randomized data and guidelines.

And so I think it's not appropriate for this community to just sort of sit back and say, 'Well, we did the trials, therefore, everybody should do this.' But we have to look at ways in which guidelines can be implemented. And it's important not just for this specific guideline, but for guidelines in general.

And I'll point to two quick models. One is from Vermont -University of Vermont, where they were able to use an electronic alert to identify high-risk patients, and those patients are referred to a service comprising of pharmacists, and advanced practice providers who then educate the patient about DVT/PE, risk and recommend prophylaxis. And with this alert, 94% of patients went on prophylaxis. So it's not that it can't be done or the patients are resistant or providers are resistant, it's just that we have to have the infrastructure in place to be able to do this. A second model is currently being piloted here at my institution, the Cleveland Clinic, we don't have data on that, but it also uses a similar electronic alert to warn providers, and then a link to a prescription to be able to send a prescription out.

Dr. Connors:
So that's an impressive model. Because I think the first at Vermont's requires administration support for staffing. But this second electronic alert model seems to require less staff, although you might put more of a burden on the individual provider. But that sounds wonderful in a way to bring the data to the practicing clinician, and I don't want to say force them to adhere to guidelines, but perhaps enhance their ability during their busy day.

Cihan, I don't know if you want to say anything more about prophylaxis and room for improvement as we move forward?

Dr. Ay:
I think there is a lot of research to really facilitate prophylaxis. So there is even approaches to improve risk assessment to develop novel risk assessment model to select even much higher-risk patients. So this could be one way. But there is already a very clear, I mean, data that we have here. And maybe with regard to guidelines coming back to the guidelines, I think, having worked in some of the guidelines and guideline developments, what I like in guidelines is also that next to the evidence that is extracted, they also identify gaps in the evidence, so - and where we should maybe do more work to improve where we need more data and

information here. Maybe this is also very important to highlight the value of the guidelines here. I don't know what you think.

Dr. Connors:
Yeah. No, I agree. I think when you're writing guidelines and we're following strict methodology, you realize, as you said Cihan, the gaps or the holes in the data in areas where more work is needed. And although guidance statements can be written, based on say, expert opinion, it's not the same as having that gold standard randomized controlled data.

So I look forward to seeing data from both of you in the future on these aspects of cancer-associated VT care. And on behalf of myself and my colleagues, Dr. Alok Khorana, Dr. Cihan Ay, I'd like to thank you for attending and watching our roundtable discussion.

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