Podcast Transcript
Cancer and thrombosis

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Tonke de Jong (COR2ED)
Currently, heparins and/or DOACs are safe and efficient at treating thrombosis in cancer patients. However, what about primary thromboprophylaxis in cancer patients? Keep listening to find out. Thank you for listening to this podcast episode from COR2ED independent medical education. The podcast is supported by an independent educational grant from Viatris. This podcast series focuses on thrombosis in various clinical conditions and consists of 4 episodes. In the second episode experts discuss the connection between thrombosis and cancer. You will hear internationally renowned experts Prof. Dimitrios Tsakiris and Dr Lars Asmis discuss these matters and provide their opinion on how to manage both diseases simultaneously.

Prof. Dimitrios Tsakiris
Good morning, everybody. My name is Dimitrios Tsakiris, and I am a haematologist from the University of Basel in Switzerland, specialising in clinical and diagnostic haemostasias. I am delighted to share with you today a podcast on the subject of cancer associated thrombosis. Myself, and my discussion partner Dr Asmis, are delighted to share that with you and we think it is important for our listeners because the podcast can help you stratify patients concerning the risk for thrombosis on the background of cancer disease and help you choose the optimal treatment in that situation.

But let me first invite in the discussion Dr Asmis. He is also a haematologist and he's also specialised in haemostasis. Dr Asmis, could you tell us, please, a few words about your field of interest?

Dr Lars Asmis
Good morning, Dimitrios. Yes, my name is Lars Asmis. I'm affiliated with the University of Zurich. I work in private practice as a haematologist specialising in coagulation. I have been interested in cancer and thrombosis for many years. We did some research projects many years ago on endothelial cells expressing tissue factor and how that can be mitigated.

Prof. Dimitrios A. Tsakiris
Thank you, Lars, for that introduction. Let us start the discussion. When we talk about cancer associated thrombosis, it is inevitable not to mention the reason why this thrombotic risk exists, and it is because the tumour acts different in these patients.

We distinguish mainly two models of the risk for thrombosis. The cancer cells have the ability to produce either tissue factor or tissue factor like substances or pro coagulants, which can activate haemostasis and trigger thrombosis. And this can be multifactorial, but it is the tumour type that drives the risk concerning its intensity. It is estimated that cancer patients have a relative risk about 5 to 6 times higher than non-cancer patients to get the thrombotic event, but depending on the tumour type, this risk can be even more variable.

Lars, could you tell us, please, a few details on the tumour types and the risk for thrombosis? Which one is more dangerous than the other, for example?

Dr Lars Asmis
Well, you mentioned the pathophysiology with cancer pro coagulant substances that can be produced by tumours. And you mentioned also the tumours that either by themselves can express tissue factors or where the human body reacting to the tumour will lead to ectopic expression of tissue factors, for instance, on endothelial cells, the project I mentioned before.

Adenocarcinomas are known to produce cancer pro coagulant substances. Almost all tumours can lead to so-called micro vesicle production. These are subcellular fragments of tumour cells which can circulate, but also the body in reaction to the tumour can lead to production of endothelial or platelet micro vesicle. So there's a multitude of mechanisms that are active.

We know that slime producing adenocarcinomas are highly pro coagulant. We know that, for instance, haematologic cancers by the associated cytokines can be incredibly pro coagulant. I am not aware of a hitlist which tumour does what the best, but these various mechanisms can interact and they can certainly be present at the same time.

Prof. Dimitrios A. Tsakiris
That is correct. I mean, 20 years ago we didn't know so much about the multitude of these reasons and causes for thrombosis.

Concerning the tumour types, there are some lists in the literature which state brain tumours or pancreatic tumours or ovarian tumours are more prone to cause thrombosis than others. But this is also, as you mentioned, patient relevant and patient dependent. But do you think the genetic background of the patient plays a role? When we talk about thrombosis, the first thing that comes in my mind as a haematologist is heritable thrombophilia. Do you think that is an additional burden? Or the tumour type overrides the risk through a thrombophilia genetic background?

Dr Lars Asmis
In preparation for this webinar I found a paper which is in print right now from the Wells Group from Canada, and they looked at classic risk factors and their interaction also with hereditary thrombophilia, and they found that amongst the classic thrombophilic risk factor, it was only factor V Leiden, which interacted with their model in increasing the VTE risk, or the cancer associated thrombosis risk, relevantly. Next to factor V Leiden, there were the people with non-blood group O that had an increased risk and these factors are not only additive, but they're more multiplicative, in a simplified version.

Prof. Dimitrios Tsakiris
That means, depending on the medical history of the patient, we can take investigation of thrombophilia into consideration and choose wisely whether we need it or we don't.

But let me go to the more attractive part of our discussion, which is treatment. When thrombosis is present you need to treat it. And treating it is a, let's say, complex action, because these patients are not the same ones without cancer having a thrombosis. Now the first issue that I would like to discuss is the availability of tools that we have to predict or stratify the risk for thrombosis and categorise patients in thrombotic or more thrombotic or less thrombotic. I have found in the literature about seven or eight different published scores which handle prediction of the risk for thrombosis, but only few of them, for example the Khorana score or the Vienna score and the Pabinger score are prospectively validated in clinical studies. What is your experience on the use of scores first and second, do you have a preference concerning a score?

Dr Lars Asmis
Well, I think there are several scores that have been validated, as you have mentioned, depending on which study you tend to want to go to. You can argue that the Khorana score is validated. You can argue that the Vienna score is validated and also that, for instance, at the PROTECHT Score is validated. But again, this is not an exclusive list.

I have some problems with these scores, or I prefer not to only use a score in assessing the risk and I will come back to that in a second. These scores, they tend to have variables that are used to assess the risk that either are not available in regular medicine, for instance, the Vienna score has P-selectin as a parameter. That's great in a research setting, but we don't get that on a daily basis in any clinical laboratory. The Khorana score actually only includes one known, validated predictive VTE risk factor, the body mass index. The other parameters like platelet count, like the tumour type and the pre chemotherapy haemoglobin levels, those are not classic VTE risk factors that are included in there. So yes, on a statistical level, that may work, but as an only feature I tend to say that it is of limited value.

So my conclusion is that I use the clinical assessment or my estimation of the basal VTE risk and in that I look at patient age, patient body mass index, patient previous history of VTE, family history of VTE, if known, thrombophilic conditions. And I try to integrate that into the entire equation. So I try to combine a known risk score with clinical or experience based assessment.

Prof. Dimitrios Tsakiris
Yes, thank you for that. But still some score, for example, the Khorana score, has come into the guidelines concerning indication for treatment in outpatients with cancer and chemotherapy. Now, here, would you like to comment a little bit, is there a difference between a hospitalised cancer patient and an ambulatory outpatient? Why do we have clear guidelines, clear indications for treatment concerning in-house patients, whereas the ambulatory outpatients with chemotherapy are not included, at least concerning general type of cancer, are not included in the guidelines for primary thromboprophylaxis? Could you comment a little bit?

Dr Lars Asmis
With pleasure. I think that has to do with habits of doctors, which can be very difficult to change. Oncologists, maybe more than than haematologists who work a lot with coagulation, they are reluctant to introduce a VTE prophylaxis. They, in my view, are much easier in giving a relatively potent and efficient chemotherapeutic agent to a patient, even by IV infusion or subcutaneously, long before they might agree to giving a low molecular weight heparin to their patient on a longer basis.

This is a perception on my side, but there's actually also some published data on this. And I think once a patient is in the hospital, then doctors can more readily accept the fact that they need a VTE prophylaxis, whereas once they're on an ambulatory basis, then they're hesitant to do so. This in part also may have to do with the fact that low molecular weight heparins had to be injected and now with the direct oral anticoagulants, we have alternatives to that. But that, in my perception, has not led to a generalised acceptance of the fact that VTE risk in cancer patients can be so high that it may necessitate or may justify a primary VTE prophylaxis.

Prof. Dimitrios Tsakiris
Yes, that is correct. In my experience, also oncologists have been more reserved concerning this issue, but they are urged now by, for example, the guidelines of the American Society of Clinical Oncology, to at least inform their patients on the risks for thrombosis and under certain circumstances on the tumour type and prediction risk with the Khorana score, primary prophylaxis is indicated either with low molecular weight heparins or with the newer direct anticoagulants.

But let's go back to the established thrombosis. You have a tumour patient and he gets a thrombosis. So we have to treat him. And traditionally low molecular weight heparin is already, from the time of the ‘milestone’ study, the CLOT study more than 30 years ago, and was medication of first choice on that. In the meantime, the newer direct coagulants came in use. And they were initially tested in registry studies in general patients and then

successfully at the end in focused patients with cancer, the disease and they were efficient and safe. Now, how do we choose? Do we give these patients low molecular heparins or do we give them DOACs? What is your experience in that Lars?

Dr Lars Asmis
Well, I criticised the oncologists for being slow in changing their habits. I have to admit I'm equally slow in changing certain habits. I'm a great fan of the CLOT study from 2003. It was designed as a superiority study. It looked at recurrent VTE and the relevant parameter over symptomatic VTE. All of the studies done in direct oral anticoagulants were laid out as non-inferiority studies. They also included incidental VTE, and there were several other factors that make these studies difficult to compare.

To make a long message short, in my personal view, low molecular weight heparins are still the prime modality to treat cancer associated VTE. I'm well aware of the guidelines and the meta-analyses which now say that DOACs treat cancer associated VTE better than the low molecular weight heparins, at the price of having an increased bleeding risk.

Again, there's a strategy from the author of the CLOT study, Agnes Lee, which I find very usable and which I try to adhere to, where you have a three staged approach. First, you look at bleeding risk. What is the bleeding risk in my patient? You look at the medical interaction. So the interactions with potential tumour therapy, would there be a problem? And the third is also the tumour type that is involved in case of gastrointestinal or a urologic cancers, cancer forms which were mostly excluded or underrepresented in the DOAC cancer associated thrombotic studies.

So if any of these three aspects are met, then you go fall back on low molecular weight heparins. If they are not met, then you can certainly start with a direct oral anticoagulant of your choice. So that's the approach that I adapt or that I use from Agnes Lee.

Prof. Dimitrios Tsakiris
That is correct. That proposal from Agnes Lee is very illustrative and very easy to digest and also easy to apply. But still you have patients which cannot come under the same condition. What do you do with thrombocytopenia, for example? What do you do with the duration of the study? How long do you treat with low molecular weight heparins? The CLOT study did not have extensive durations. How do you handle this?

Dr Lars Asmis
Well, the treatment duration is an excellent question. For six months we have solid data, three to six months in CLOT study and also in the DOAC studies. After six months, we just don't know. As Armand Trousseau who is basically the founder of the cancer associated thrombosis said, doctors should not hesitate to admit their ignorance.

We don't know what the optimum treatment duration is, period. So we can adapt, we can talk to our patients, we can include patient preference, we can look at, for instance, dose reducing steps. For instance, in the CLOT study, the original low molecular weight heparin dose was 200 international units and later on you went down to 150. Similarly, there is data outside the cancer setting where for apixaban and rivaroxaban, one can use half therapeutic

levels at an acceptable risk benefit for bleeding and thrombosis prevention ratios. Maybe, I don't know, maybe these reduced doses will also work in a cancer setting. We don't know. There are studies ongoing which might help us in that.

Prof. Dimitrios Tsakiris
Yes, but in general, I think though, that as long as the tumour is present, treatment should continue.

Dr Lars Asmis
I agree treatment should continue. But at which dose? That is the point I'd like to make. Maybe we do not need a therapeutic dose. Again, I don't have proof of that in the cancer setting for the direct oral anticoagulants, but it would be a very interesting target or interesting study context to look at.

Prof. Dimitrios Tsakiris
Now, I would like to touch this point before we are coming to the end of the podcast. Two marginal issues which seem interesting. More and more literature is coming in publication lately on the issue of onco-cardiology. That these patients with tumours having cardiological heart disease. For example, a typical patient with heart disease who would need anticoagulation is an atrial fibrillation patient and we know, or at least the literature reports, that tumour treatments and the tumour itself, are considered to be triggering factors for atrial fibrillation. Now, how do you treat atrial fibrillation in a tumour patient? Do you give him low molecular weight heparin as you do because of the tumour, or do you give him DOACs, which is the standard choice for atrial fibrillation outside the tumour spectrum? But still patients treated with DOACs have some restrictions concerning choice of drug because gastrointestinal tumours are excluded from that indication or patients with a bleeding tendency, are excluded from that indication. So what do we do is the issue. We don't know because concerning atrial fibrillation in tumour patients is an open issue still. We don't have the focused prospective studies that can handle these. Could you tell us if you worked on that, Lars, please?

Dr Lars Asmis
I will try. So your question was, how do we treat these patients? I would say very carefully. So increased supervision, increased surveillance, I think is the A and O in these patients. Renal insufficiency is more frequent in cancer patients and plays a role in DOAC treatment so we need to look at these factors. We need to look at the liver metabolism. DOAC plus single cancer therapy, there's a paper from Cihan Ay from Vienna, states that in very few instances will there be a relevant interaction between the direct oral anticoagulant and the tumour therapy. But my response to that would be as soon as there are other CYP3A4 metabolites or metabolise drugs in the equation, so if these patients start to get psychotherapies or neuroleptic or sleeping medications that may interact with the cytochrome P450 pathways, then we may be more prone to measure an anti-factor Xa or an anti-factor IIa, depending on the DOAC that we use.

So we just need to be more aware of what's going on in our patient. We need to survey the relevant parameters, including renal and liver function and also the interactions which may occur on a CYP3A4 or other basis.

Prof. Dimitrios Tsakiris
Thank you for that. We don't have much time left, but I would like just to touch relative subject, which is not relevant any more in my opinion, but you might have a different view on that, the possible anti-tumour effect of anticoagulation. At the time of the CLOT study 20 years ago, there was a possible antitumour effect reported in patients who had not extensive disease. Later on focused studies did not support this, did not confirm this, and the discussion on the antitumour effect was abandoned. Could you tell us, in one sentence please because we are short of time, do you agree with that or do you see other ways out of that?

Dr Lars Asmis
Again, in that I am reluctant to change my habits, I do see a potential role for low molecular weight heparins in inflammatory conditions. So as soon as you have cytokines around, I think the low molecular weight heparins may be helpful. I agree with your assessment that around the 2000s there were meta-analyses, clearly showing an improved survival. In the 2010s these meta-analyses started to change their formulations and in 2016 I believe I saw a meta-analysis that says that the survival effect can no longer be shown, but that an anti-metastatic effect may still be there. I think the context has changed, whereas previously patients weren't exposed to low molecular weight heparins, nowadays they much more are. This may be a confounder that we lose this effect in the meta-analyses. The proper study I haven't seen to prove the yes or no. I'm a big fan of low molecular weight heparins based on the fact that they are a mixture of molecules which have all kinds of binding targets. I like to believe that they do play a role, particularly in inflammatory or inflammation associated conditions.

Prof. Dimitrios Tsakiris
Thank you Lars for that. So we have come to the end of this podcast. Before we close, I would like to give you two key takeaways to keep in mind. First, heparins and/or DOACs are safe and efficient in treating thrombosis in cancer patients. And second, primary thromboprophylaxis is efficient in selected cancer patients, but still remains a matter of debate for the majority of the tumours. Lars, would you like to add a last word?

Dr Lars Asmis
I completely agree with your conclusions. In addition, I would like to focus on the importance of talking with your patients, including patient preference in the treatment plan and by doing that, I think we can greatly improve the quality of life in the cancer associated context.

Prof. Dimitrios Tsakiris
Thank you Lars for these contributions in the discussion. Thank you listeners, for being with us today. Thank you.

Tonke de Jong
We hope you enjoyed the second podcast episode in this series on thrombosis in various clinical conditions. If you liked this episode, look out for more episodes in the series on the COR2ED medical educational channel. There are three other episodes in the series where

Professor Tsakiris leads the expert discussion on anticoagulation, venous thromboembolism and peri operative thromboprophylaxis.

Also, don’t forget to rate this episode on the COR2ED website and share our Podcast on Social Media or with your colleagues. Thank you for listening and see you next time!

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