Cardiovascular Recovery in Anthracycline Cardiotoxicity

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Dr. Bell: Welcome everyone again to another of our sessions of Interviews With The Experts. I'm Malcolm Bell, Vice Chair of the Department of Cardiovascular Medicine here at Mayo Clinic of Rochester. Today, I am joined by Dr. Joerg Herrmann, who is a professor of medicine. He's also a Director of our Cardio-Oncology clinic, and he has a particular interest and certainly expertise in the management of cardio-oncology issues. Today, we're here to discuss Anthracycline cardiotoxicity. So welcome Joerg.

Dr. Herrmann: Thank you so much Dr. Bell. Excited to be here and to chat about this topic, which I think is still important.

Dr. Bell: Yes. So maybe just to start off with why we're even discussing this. Certainly looking from the outside in, there appear to have been remarkable developments in cancer therapeutics over the last year, 10, 20 years. Is it surprising that we're still using agent, you know Anthracycline agents since we've known about cardiotoxicity in these for many, many decades? And so, maybe we'll just start off with just asking you, is this surprising and if not, why are we still using these agents? Why, they must be very effective in a number of cancers.

Dr. Herrmann: Yeah, indeed. I mean, a very good question. I mean, one could ask or say in response. I mean, are we still using penicillins. I mean, we do. We've had other antibiotics coming along, and we're still using the penicillins because they're so effective. And the same holds true for Anthracyclines. Now, Adriamycin, that's one of the names for it, right? So I mean, Doxorubicin, Adriamycin comes from the Adriatic Sea. That's was in Italy where it was serendipitously discovered the whole class, in fact, and that was in the sixties. So that gives their perspective, I mean, how many decades, over half a century. And then the efficacy that really drove their use is just there. It's one of the best, I mean, cancer therapeutics out there. It's just the toxicity that you allude to, particularly, the cardiotoxicity that was soon found to be dose-limiting. So you see, if you give, I mean, they gave doses up to a thousand milligrams per meter square, unheard of. It's sort of like smoking in the beginning, right? People were smoking left and right, and then they realized that there could be some side effects to that, similar to the Anthracyclines. And it was heart failure, refractory heart failure that could even develop early on with those kind of doses. But the use has declined, particularly in breast cancer. So when we look at the breast cancer population, they don't receive a high dose to begin with. And then a lot of efforts being made to use less and less. But this being said, there still is a population of breast cancer patients for which this is still, I mean, the best therapy or the most efficacious in terms of cancer outcomes. And then hematological malignancies, leukemias, and particularly lymphomas. I mean there we have really, I mean, strong data that when we look at diffuse large-B cell lymphoma, for instance, R-CHOP is the abbreviation for what they're using. That those components, if you used all of these, that's really the best outcome yield in terms of lymphoma. And then sarcoma, that's the group that receives really the highest-dose spectrum. But again, I mean, it's an essential component there. And so, efforts have been there to reduce the use of Anthracyclines, but the bottom line is it's still a very efficacious drug to use, and is here to stay.

Dr. Bell: And is there typically a strategy to decrease the dose? I mean, compared to the historical doses and presumably with other agents that used in conjunction, also are very effective. So by decreasing the dose, you have not necessarily decreased its effectiveness. Would that be fair?

- Yeah, I mean the more is better. I think it's still what most hematologists or oncologists feel if they dose reduce in some of their regimens based off comorbidities or age. But in large part, it's sort of substitution. I mean, just, I mean taking it out completely, and substituting it with another agent, so it is a combination of both. I mean, there are efforts of dose reduction, but as well as substitution.

Dr. Bell: So maybe you could just briefly tell us, I mean, who are be the patients that would be contraindicated from the get-go? Presuming that there may be people with preexisting cardiomyopathy, but maybe there's some other risks that we need to consider. And then what sort of strategies are currently in use in terms of mitigating those side effects? And again, we're just talking about the cardiotoxic side effects, and the surveillance that is currently being used. I mean, historically, you know, we're looking at echocardiography in terms of following these patients. But are there other ways we surveil these patients today?

- Yeah, so a number of of questions here and aspects to go through, but this is really the essence of it, right? When we look at the cancer patients who's about to get this kind of therapy, we have to look at these patients from the very beginning before they even get the first drop or infusion of Anthracycline therapy. So it's the before, during, and after we're looking at for these cancer patients. And when we go back to the pathophysiology, although, I mean, I've said just over a half a century of use and research in this drug, we still don't know exactly the one precise mechanism that causes cardiotoxicity. There are a couple of aspects of how this is mediated, but one thing for certain is the impression that this is sort of irreversible injury. Once you, I mean, it kills off cardiomyocytes. And I mean, and then, I mean, that's it. And you at the end, you end up with fibrosis, sort of replacement fibrosis. And there's been studies showing that those patient who really have a prominent decline in LV mass are the ones as you can imagine, with the poorest outcome. And there is maybe a little bit of a give and take. You have the loss of cardiomyocytes and then some patients do not have the regenerative capacity to compensate for that. So I think that kind of imbalance over time is what comes out, and there are some studies looking at progenitor cells, and I mean that impairment. So a number of aspects is what I'm trying to highlight when it comes to the pathophysiology, and to be aware of. So going into this, I mean, it's only intuitive that those who have some preexisting cardiovascular disease or stress on the myocardium are the ones who would be at highest risk where any of the pathways are already stimulated. Response pathways, for instance, a nice example, are actually breast cancer patients who are getting Trastuzumab. That's a drug and antibody that was designed to take us away from the old cancer therapeutics, such as Anthracyclines with, I mean, really this kind of shotgun approach and go to the targeted therapies. But what we didn't know at the time was, that it would actually target this stress pathway in the myocardium that's activated in response to Anthracyclines. So when you combine these two, that's where you really see a lot of derangements. And there are scenarios where this pathway has already stimulated myocardial ischemia or high blood pressure. High blood pressure is one of the most prominent cardiovascular risk factors when it comes to cardiotoxicity. But patients who have a reduced

ejection fraction cardiomyopathy to begin with are obviously, already at a higher risk, 'cause the reserve is so much lower. I mean if you already, it's same as the exercise tolerance. If you started at a low level and go even lower, I mean that's not good. I mean, if you start on a high level and have the same amount of decrease, you still might come out okay at the end. So that's where 40% of an ejection fraction is commonly designated as the cutoff below, which one would not really recommend any cardiotoxic medications. Now, it's a benefit-risk discussion on an individual basis. Some patients, they might not have any alternative. It's sort of what do you wanna die from? It's almost in right to a point it way to say that I mean, it's gonna be heart failure or it's gonna be the malignancy. How can you address both? So mitigation therapies then, once you've identified and there are tools out there, for instance, the Heart Failure Society of the ESC, and the International Cardio-Oncology Society combination, they have these risk performers. We come out with a checklist, a point system and you say, I mean, you're low, intermediate, high, or very high risk, and then you should, I mean, manage this patient accordingly. That's what's also in the guidelines, the ESC 2022 Cardio-Oncology Guidelines that kind of approach. So if you have someone with a high-risk scenario, actually the one class, one indication is think of other therapies too. Before we talked about before, do you have options, substitute, or reduce the dose, or what, how can you do it? With Anthracyclines, there are other formulations with Doxorubicin for instance, there's the liposomal formulation and that, the strategy here is that it would accumulate more in the tumor tissue than in the heart tissue. That it was sort of, I mean, have a bypass on the myocardium. And that's been used in breast cancer patients in particular, Doxil, I mean it's quite extensively used. And there are good data that the incidence of cardiotoxicity is less. Another strategy, a drug, it's called Dexrazoxane, Zinecard is the trade name, that's also been used and it's in, I mean, we know it likely as an iron chelator. Or it's been used, but it also works on the second hyper main leading hypothesis for Anthracycline cardiotoxicity, which goes to top of isomerase to better inhibition. And so it works on these aspects, and there are also some good data. They initially came from the pediatric cancer population that this is very efficacious, but there are some reservations in the oncology, hematology world as they feel like drugs such as that might protect the cancer cells as much as the myocardial. So there's been that reservation, but there are these two specific strategies, which are preventive. And then beyond that, there have been studies shown that certain beta blockers, Carvedilol, Nebivolol, Hydrostatins, maybe Spironolactone would be efficacious. Though this being said, there was just a study published in the New England Journal of Medicine, evidence that new sub-journal of the New England Journal of Medicine, and it was a study looking at that patients undergoing Anthracycline-based therapy have no indication for statin therapy whatsoever otherwise than just the cardioprotection. Is it efficacious? It was Atorvastatin 40 milligrams and the results were negative. It wasn't efficacious to just give statins for the purpose of cardiotoxicity protection with Anthracyclines. So those are sort of the evolving field of mitigation prevention strategies. And then if you pursue these, and even if you don't pursue these, but I mean, you should wanna know, I mean, is there some cardiotoxicity developing? 'Cause we also know the earlier you detect this and the sooner you react to this, the better are the outcomes. But that's another maybe, a follow up question as far as how should be monitored.

Dr. Bell: So let me interrupt you. I mean, that's really fascinating, and it's good to hear that there are a lot of these strategies using different agents that maybe slightly different targets there. But let's just take a patient who's not considered high risk, you know, it could be a young woman or young man, normal cardiac function is being treated with these agents. And presumably, if they

did develop a cardiomyopathy, these strategies would then be implemented that just as they would be for a high-risk patient if I'm understanding you correctly. But what I'd really like to know is what's the earliest you could detect this, before you see a significant decrease in LV function, and then particularly left ventricular ejection fraction? What type of imaging you is best suited for to pick this up early? And are there biomarkers or any other markers that would alert you that they're in the early stages of developing cardiotoxicity, so that you could put into place those mitigating strategies?

Dr. Herrmann: Mm-hmm. No, very good question. Indeed, so the biomarkers that have been proposed, the usual culprits, right? Tropronins and BNP. Troproin, particularly useful during the cancer therapy, I mean, at the time of acute injury, and then sort of their value levels off. Whereas BNP might be the opposite. I mean, where you see maybe not so much of a signal early on, but later on, it emerges in their survivorship. And then for, I mean, the mainstay though that's been pursued is echocardiography and strain imaging, so abnormalities in Global Longitudinal Strain as being the most sensitive marker. And there was a trial called the SUCCOUR trial that looked at that. I mean, what is the value of reacting to early changes in strain? Now they used a relative change as a cutoff of just 12% relative change, which is a relatively sensitive action when you think about it. So you need to have a good echo lab for once. I mean, you need to have a, I mean, a good echo lab with reliable strain-imaging analyses and a good baseline assessment. And sometimes it's not so easy. Some of the breast cancer patients, for instance, after mastectomy or for some other reasons, I mean, it's not so easy to image them, but echo imaging, strain imaging has been the main thing. And there was, even though the SUCCOUR trial, when you just look at EF base versus strain imaging, there was the primary endpoint did not differ. There was a signal that if you detect changes earlier with strain imaging, patients tend to have a better outcome in terms of.

Dr. Bell: We just got a couple of minutes left here, just staying on imaging. What about is there a role for cardiac MRI and then particularly in patients who echo may be physically uncomfortable for them?

Dr. Herrmann: Mm-hmm. Sure. That's been also looked at cardiac MRI. And the same, you can also do some strain assessment on cardiac MRI and get, I mean, the same information. And in general, these more sensitive markers do indicate change a couple months earlier before you see it in the f, although critics have said, and I might consider myself as a critic, sometimes you can already see the writing on the wall, even if just looking at the f change. It might reach significance when you because of a higher standard deviation, but I mean, it's already, the message is already there.

Dr. Bell: Okay. But there's no other signals that you might see in cardiac MRI just in terms of attenuation that would tip you off that this was in the early stages. So with a patient who develops signs of cardiotoxicity, you talked about mitigating strategies. Let's assume that they've finished their, you know, chemotherapy regimen that at least your first time round, but they're left with LV dysfunction, presumably that's gonna be treated in the same way as we would treat any patient with significant left ventricular dysfunction. You know, in terms of medical therapy, is it reversible? Is the expectation that this might improve in the future? What can you tell us about that just in our closing minute or so?

Dr. Herrmann: Yeah, no, that's very important. I mean, a lot of attention has been paid to the before and during, but then the after, and how you deal with these patients. And the assumption has been, yeah, why don't we just give standard heart failure cardiomyopathy therapy, beta blockers, and ACE inhibitors? But the important aspect is and to highlight that it, only 10%, 11% was the actual figure really have a complete recovery in their ejection fraction. That's not a whole lot, right? 90% only partial recovery and then maybe even 20% there's no recovery in the response to these standard drugs. And it takes a long time. It almost takes a year for them to come back over the 50% mark. So the standard therapies, I mean, while they're applied, may not be the best solution. It's what we've always had. So here at Mayo, because in our translational, and multidisciplinary approach with basic scientists, clinicians, we've worked in this and looked at this, and Dr. Xu who's of our basic scientists, I mean he has a lot of experience with zebrafish. He did a very fascinating work and catalog after an initial signal was found related to the mTOR pathway and autophagy, looking at drugs that are already out there, and have them autophagy-activating effects, and could be repurposed. So FDA-approved, autophagy-activating drugs that could be repurposed. And there were two main hits, and those were actually Pravastatin and Spironolactone. So those were the two that, and we tested that then in a mouse model. And these two worked better than Carvedilol and Lisinopril, which only showed some mild benefit. So there might be something to this, and points to the direction, again, here at Mayo Clinic, we have a key interest in this biomedical discovery, and bringing the bench to the bedside. I mean, right? I mean to come from a pathophysiological understanding is what the mechanisms are. I mean, addressing them in this way with novel therapies improve the outcome of patients. So there is something new on the horizon, I would say, and it's very much needed. It's sort of the afterthought after therapy.

Dr. Bell: So I think it's fair to say then that, I mean, these efforts are really gonna be very important and obviously worth it for drugs that are very, very effective in treating cancer patients. And I think also as you began to stress, having a very good echocardiography lab, and the collaboration between your oncologists and cardiologists such as yourself, you know, in a specialized clinic of cardio-oncology is really important to really avoid your complications. And so that, and treat them if they arise, and very important in terms of those, you know, mitigating strategies so that those patients really can get the very best treatment for their cancer. I don't know if you have any other closing words, but I think there's been a lot of information shared here. It's really fascinating and obviously these drugs are gonna be around for a lot longer, and hopefully we can decrease the risk of toxicity and treat these patients appropriately.

Dr. Herrmann: No, yeah, thank you so much. Couldn't be summarized any better. I mean, you sound like a cardio-oncologist.

Dr. Bell: I don't think so, Joerg. All right. Well listen, Dr. Herrmann, thank you so much, again for sharing your experience and expertise in this area. And thanks for everyone for joining us today.

Dr. Herrmann: Thanks.

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