ICI Myocarditis

Announcer: Welcome back to the Mayo Clinic cardiovascular podcast series, interviews with the experts. I'm your host, Sharonne Hayes. I'm a noninvasive cardiologist and vice chair of faculty development and academic advancement for the Department of Cardiovascular Medicine here in Rochester, Minnesota. Today I'm joined by Dr. Joerg Hermann who is professor of medicine, chair of research for the Ischemic heart disease program, and director of the Cardio-Oncology Program here at Mayo Clinic in Rochester, Minnesota. So today our topic is ICI myocarditis. Dr. Hermann will share with us the evolving use of immune checkpoint inhibitors or ICIs and their cardiovascular side effects, including myocarditis, heart failure, and coronary events. We'll also discuss current challenges in the diagnosis and treatment. So Joerg what are ICIs and for which diseases are they being used? We know cancer, but maybe there's some other things you wanna share.

Dr. Joerg Hermann: Yeah, thank you so much Dr. Hayes for the introduction. And I'm truly excited to be here and to talk about this topic, which I believe will become more and more important even for the general cardiologist, even the general internist, because these are really sort of block blockbuster drugs, right? I mean, they, they weren't there a couple years ago. We didn't learn about them in medical school. And, and so yeah, immune checkpoints, what are those? And so I grew up in Germany, right? And, and it was east and west and there was this famous checkpoint, Charlie, so between east and west Berlin, and you had to show your passport. And if you didn't have any of that flak, you get get shot, right? I mean, potentially. And so if you try to intrude, and so it's the same thing with our immune system. And so they, they surveil and they get activated, but then there are mechanisms in place to keep them in check. And they're on two levels. So the first level is on the level of the thymus. It's the central regulation. And there is a pathway that's called CTLA four. It sounds fancy, but it's just an abbreviation CTLA four. And so that's one pathway for silencing. And then the other is more in the periphery. And that's the program death pathway. PD one, PD L one, PD one is expressed on T cells, PD L one, the ligand for it is expressed on, on peripheral tissues, including tumor cells. And it's very fascinating that we, Sharonne, 'cause we have one of the inventors of this here at Mayo Clinic. His name is Dr. Dong, Dr. Haidong Dong. And so he's from China and he said he was given this research project, his, his mentor gave him his research project, why don't you look at two more tissue? And he said, so I looked at the two more tissue and what I noticed were these black around it. And I was wondering what are these cells and, and why they're sort of paralyzed. And these were then turned out to be T cells surrounding the tumor and being really paralyzed. So that was, I mean, the PD one, PD l one story that he contributed to it was not like Jim Allison or Tasuku Honjo who got the Nobel Prize in 2018. But you can see that's where it lets, so immune checkpoint inhibitors, to answer your question, I mean are those pathways that are, are, are negative feedback loops built in to avoid overshooting immune reactions. And tumor cells have, in a sneaky way used this mechanism to silence those, those tumor attacking T cells and, and forego their, their detriment.

Dr. Sharonne Hayes: Mainly cancer. And we know that there are side effects. I, you know, I certainly, this is not something I learned about during training, but when I am covering the consult service at our hospital that houses most of the cancer patients we're asked to weigh in on this all the time. So yes, it's already affecting us general cardiologists. What are the most common side effects, particularly cardiac and, and what do we need to be watching for? Or will we be asked to weigh in on?

Dr. Joerg Hermann: Yeah, so the, I mean, you might have heard, I mean like, 'cause I mean, as I said, I alluded to, I mean, there's a lot of excitement about these drugs, right? I mean, and, and for some patients, particularly when they introduced first from melanoma patients and non-small cell lung cancer patients. I mean, those were like the biggest groups. I mean there was, I mean, a lot of excitement. Christian Bernard, he said this with a heart transplant, right? I mean, I mean, when are you willing to take such risks? And, and so if a lion chases you to the rink, to the bank of a river full of crocodiles, I mean, you live in there gathering that you have a chance to survive. But I mean, but the odds are very slim. Now, what are the odds of having side effects with these kind of drugs? So some reports would say up to 90% of patients might have immune related adverse events. And I think when, when, when you look at systematic reviews, it might be more than two thirds have have really an immune related adverse events. And in 15 to 20% it's severe, clinically relevant. So that's still a fair number of, of, of, of patients. And the most common one are skin related rash. Second is gut, so diarrhea, colitis. And the third is endocrine. Any, any, any endocrine organ. So all the itis you can think of, adrenal neuritis, hypophysitis, thyroiditis, you name it, any itis. And then from a cardiovascular disease spectrum, they're, they're sort of on the lower hole there. But nevertheless, myocarditis, I mean, has made the news because of its fatality rate. I mean it's, we think it's just 1% of patients who might develop myocarditis with these drugs. But then the fatality rate in the neural reports was 60% up to that. I mean, in terms of an, of an estimate. Now we often, I mean particularly early on when, when Javid Moslehi and others mean reported on this, it was just two cases, right? Reported in the New England Journal of Medicine. They worked it up very thoroughly. But that was the very tip of the iceberg as Fulminant in myocarditis and as it often is in these field. And these drugs get rolled out. And then, I mean, the most severe cases, they make the news. So Fulminant myocarditis, we've learned about. But since then we've realized that there is such a spectrum of the inflammatory entities in the myocardium. With this, you can have my myocarditis pericarditis, myo pericarditis. You can have inflammation of the myocardium without much of myocyte loss. You can have myocyte loss without much inflammation. So there is, there's a whole spectrum. And, and that I think is generating the problem for us on the consult service or when we see these patients, it's like, how do we interpret this? 'cause I mean the, the common denominator is troponin elevation, isn't it? I mean, nowadays, I mean everyone, and then we can talk later a little bit maybe about these surveillance process protocols. Does it make sense? I mean the, I mean to surveil patients with troponin serially for this possibility, but nevertheless, I mean, if the patients show up on our service or we get even outpatient clinic because someone checked the troponin, then yeah, how do we interpret this? And we gotta be aware of the fact that there can also be coronary artery disease. It can be an acute coronary syndrome. Still, there are some studies suggesting that it's not only myocarditis, that there is an acceleration of atherosclerosis possibly, or vulnerability of atherosclerosis. And then the arrhythmias that can occur too, SVTs atrial fibrillation. So you can see, see, see those as well. So it's not always myocarditis and what from, from animal experiments has come out. And, and this is from, from a former place of training in, in Germany, in essence, what they found was in mice it's really hard. They're really resilient to cause myo to get myocarditis with these drugs. But what they got consistently was cardiomyopathy, especially in the presence of a tumor implanted in these mice. And that's what another group in, in live and Belgium saw as well. It was not myocarditis, it was heart failure, it was cardiomyopathy. That really is something they've noticed. And, and what was also to a degree concerning is in half of these patients, it was after ICI therapy had been stopped. So there's another to this, it might not be actually right at the time. It might be some delay in, in seeing these, these effects. So

we always been taught it's coming on through the first three cycles of ICI myocarditis maybe, but cardiomyopathy can be later. And you can also have takotsubo by the way. But I, I let you weigh in on me. 'cause that was a lot of information already. I assume

Dr. Sharonne Hayes: It was. So, so you know, I think what, what I've heard from you is there's some really pleomorphic effects, pleotropic effects on the heart. And we do not fully understand them. And we're still learning if we focus in on the myocarditis, and you said kind of universally they have elevated troponins or that's one. But how do we di you know, is this somebody we should be surveilling or are, are most of these people coming in sick? And how are we gonna approach the diagnosis of this, you know, as opposed to acute coronary syndrome. Just tell us how, what is your approach to start diagnosing?

Dr. Joerg Hermann: Yeah, so I mean there there are different criteria that we've come up with. So the, the International Cardio-Oncology Society, and then it went into the European guidelines, the European Society of Cardiology guidelines, where we developed the definition of ICI myocarditis. There was a prior grit of, of probable possible and definite myocarditis that folks have come up with. The, the usual players for both of these are the biomarkers are the ECG changes are the imaging studies and then the clinical syndrome. So I think often it starts with a clinical syndrome, but myocarditis is sometimes really hard to pinpoint of, sure, it can have some chest discomfort, but what else is there? I mean, arrhythmias have been some of the leading points, right? I mean, you can have, I mean, the first case we've seen here that that was classic. That person had alternating bundle branch block, complete heart block, non-sustained vt. I mean, the whole spectrum of what you can see with these arrhythmias and in expression of the irritability of the myocardium. But you may not see that, I mean, atrial fibrillation, we've looked at that it may signal some inflammation, but it may not, it's not like a, a perfect predictor of that's being present. Now the, the chances of this do go up if patients, for instance, have myositis and then there is the, the neurotoxicity to this or the myasthenia gravis. So that's known as the Triple M, right? Myasthenia gravis, myositis myocarditis, that's the Triple M. And those patients, they're at high risk of adverse outcomes including mortality. So that's, that's often, so having some other immune related adverse events that really brings up the probability that we're dealing with this. And then from an imaging perspective, we, we've, we've looked at strain imaging. Sure there are these reports from registry based studies that they indicate possibly indicate myocarditis, but they're not perfect then cardiac MRI and much to the surprise many, I mean, that's not perfect either. I mean, so if you have a positive MRI you're done. But if you have a negative, cardiac MRI, that doesn't exclude the possibility of myocarditis still. So the first patient with all the manifestations he had, he had two MRIs that were negative. And we've seen other cases too. So Tom Neland from MGAs who, who, who studied this very carefully, he reported that an initial so early cardiac MRI might miss it and a late cardiac MRI might miss it. So there is sort of like an optimum timeframe, but how do you pin that timeframe? So what the recommendation has been, and I think we may not do this enough, and so that will answer also the question about the value of troponin surveillances as a reference, the car end of myocardial biopsy. 'cause we've, I mean, so that, I mean, we've been surprised again and again of the seemingly negative by imaging criteria, even echo not showing much, right? But then the biopsy comes back clearly positive for myocarditis. So I think as a clinician, if you have the smell of myocarditis in, in, in your nose, I think you've gotta pursue it. And

you've gotta be bold and, and ask your interventional cardiologist if they wouldn't mind doing a biopsy in these patients. Now you can miss it too, but I think Sharon, I think you really have to be a little bit more aggressive in some of these cases where everything points to it, but we can't possibly define it.

Dr. Sharonne Hayes: So biomarkers imaging probably sounds like echo and cardiac MRI and if that gives you your diagnosis, but if not, moving on to, to tissue evaluation,

Dr. Joerg Hermann: Right? Yeah, yeah, clearly. And I mean the biomarkers, I mean they're, they're likely very sensitive, right? I mean, nowadays, high sensitive troponin, nothing escapes the high sensitive troponin, but the, the specificity is, is an issue. And then there's been this debate, I mean, what's better troponin t or troponin I? now, I mean you can, I mean some have their favorites as you can imagine. There've been, I mean, troponin t has some scrutiny because folks have reported that with myocytes in these patients you can have significant troponin elevations alone. And so we use the still, I mean like CK has been used A-S-T-A-L-T, these all liver enzymes. There are also AST expressed in the, in the muscle. And so that's been, that's been a little bit of the challenge. I mean, and that's, that jury is not fully out. If troponin i is a better cardiac biomarker, than troponin t and either way I think it's the degree of elevation. So that has been shown again and again, if you have significant elevation, some say more than two of the upper limit of normal, but where do you want to draw the line if you have, I mean you get, again, you get the smell in your nose. If you have severe elevation, that's a marker for adverse outcomes as well.

Dr. Sharonne Hayes: So let's, let's say I smelled it, I diagnosed it. Now what do I do for this patient? How do I treat them? What do they, what do I need to do and be thinking about so that we can stop it or even reverse the process.

Dr. Joerg Hermann: Yeah. Right. So if, I mean, there's been a, as you can imagine, a bait around this as well. I mean, some say, well, do you really want to give steroids to everyone? Because that's been sort of a reflex, right? I mean, I mean you see, I mean it, so like you, you see a snake in front of you, you get the revolver out and just shoot it. I mean, is it the same here And then, or, or, or some would say you just give one high dose methyl prednisolone one dose and just have the, continue the workup. Others would say, as the guidelines do recommend, you give at least three doses. So three days or three to five days. I mean, you really try to silence that, that that immune response. Now unfortunately, there are some patients who are, who are steroid resistant, they might not respond to it, that troponins may not decrease, there might not be a silencing of the arrhythmic events or other clinical manifestations. So that's usually how you gear. I mean, if your therapy is working and, and then you, you have to revert to other, to other meets. And I think where this is happening, then if there are, I mean any significant arrhythmias, respiratory distress, if you have evidence of circulatory failure, cardiac dysfunction, these patients, I mean, may need to, I mean, should go to the ICU 'cause where you feel like, I mean this is escalating maybe potentially much more quickly. So that's, that's definite the other patient's telemetry unit. But then you have those two where you feel like, hmm, I mean there, this, this, I mean myocarditis,

I mean we, we do these steroids and then you just linger and linger. And people ask can they be also managed outpatient? I mean some patients will even refuse. Sure, you may not believe it, but some patients refuse to go to the hospital. They say, I'm not convinced. I feel well, I mean I have a biomarker elevation. You think I have myocarditis? I mean, but what I mean, so they're really in the river with the crocodiles, but they don't worry.

Dr. Sharonne Hayes: It's true because many of these folks have been in the hospital so many times that, and they're not gonna go just because a blood test is abnormal. Right? I mean there's a resistance to being a sick person, especially if these drugs have been helping them. Right? Right.

Dr. Joerg Hermann: Exactly. Exactly. Right. And so if the, so if you feel like with the steroids, I mean you keep them, you keep them in check literally for these checkpoint related events. If, if that fails, then other immunosuppressive agents, right? So we've, I mean everything has been tried. We don't have any randomized clinical trials published or available that will guide us one way or another. There are two efforts though in place. There is a study in, in on the going in Paris and there is a study here, which we're part of the atrium trial. It's with Abatacept, so that's a CTL four. I mentioned this earlier and I mentioned it on purpose 'cause it's in CTL four IG fusion protein. So it's a large molecule that's, that's administered and that's, that's, it's a dco. So it's a CD 80, CD 86 decoy. So that keeps the t-cell sort of in an anergic state. 'cause I mean there are receptors are occupied, they cannot have the CD 28 mediators co-stimulation. So then, I mean there's, I mean it just keeps them at bay. It keeps them at check. The problem with abatacept is it's a large molecule, the distribution and so forth, it takes time till it really comes to full effect. And so what the group from Paris has, has published is that in these patients who also have, I mean this, I mean concerns for our grade three or high dose, so clinically very relevant events plus respiratory distress and so forth, you're worried about abatacept plus a JAK inhibitor ruxolitinib. And that's been used in rheumatoid arthritis. So that's something to, to dial down the T-cell as well as a, I mean a quicker onset. So that's been tried. And, and so they're looking into this from a, from in, in Paris further our study here that where Tom Neland is leading from MGH is the, is the, is just abatacept. And they get multiple doses for patients with, with immune checkpoint inhibitor, myocarditis as also a rescue arm. But that's sort of, I think what, in terms of evidence base, that's where means something is emergent otherwise, I mean you can, I mean you can do whatever you would do almost like for a transplant rejection, acute rejection, right.

Dr. Sharonne Hayes: You're just gonna throw everything at it right. In a sense. And hopefully have somebody like you who can be coaching us.

Dr. Joerg Hermann: Yeah.

Dr. Sharonne Hayes: Let's say their arrhythmias have settled down, the, their biomarkers are dropping, this class of drugs was working for them, their tumor was stabilized or, or regressing. Can we consider ever starting an ICA again?

Dr. Joerg Hermann: Yeah. So it's, it's, it's between you and the patient way, right? So we're in this triad, then we have the patient, we should be in the center and we have the oncologist or a hematologist, and then we have the cardiologist. And it's sort of like a joint, I mean decision. What do we advise? And we've been in these scenarios. I mean, number of people have and, and true. So I mean, if you have a clinically relevant event, I mean common guidance would be not to them. I mean, if you have, I mean, myocarditis and, and if you've had that diagnosis, but yeah, but I mean, if, if that's the only drug that's left, I mean, do you again jump into the river full of crocodiles or do you not? Right. I mean they came really close, but do you still have a, have a chance there? And so there have been some case reports on rechallenge in patients with myocarditis. That was one last year from, from the group in Zurich. And, and so what happened, what you assume what happened, I mean, they had another immune response and this time it was more aggravated than before, but no clinical events. But still, I mean, I think it's really in that scenario, I mean there's, I mean, and going back and forth through these flares of myocarditis and there's silence and I mean this, this can be good. We don't know yet at this point what is the long-term sql, I mean for, I mean the duration of this, number one, what we've seen, depending on the extent of myocarditis, it can take several weeks, several months even for it to fully silence. If you, I mean if you follow cardiac troponin level, we followed patients on pet like a, like a sarcoid protocol pet. That's something like someone might entertain as well. And so we've seen that it takes quite some time if you have significant myocarditis to fully resolve. And I don't think it's not imaginable in a way to just immune, to resume immune checkpoint therapy if, if you're still in that, in that state. And I think it's really, I mean the risks and the benefits at that point, I think it's really, I mean, but the patients, I mean, you're absolutely right. I mean, the patients will ask you, I mean in essence, I mean, what do you want me to die from my cancer, right? Or mean the, the, the adverse effects of the, of the, of the therapies. And, and that is so hard. And I think for, for us, it's really the mantra. First do no harm. I think we feel bad if, if because of a therapy we've provided, we've accelerated something. So I think that's really ethically, it's really challenging.

Dr. Sharonne Hayes: Are there other cardiovascular side effects I that we should be aware of other than the myocarditis? You've sort of mentioned just heart failure without inflammation. What, what are the things that we ought to have also in the back of our mind when we're called to see this sick patient on the oncology floor or in the outpatient?

Dr. Joerg Hermann: Yeah, so if, if it's truly not myocarditis, I mean by, by any means available to make that diagnosis, including, I mean, or excluding it, but cardiomyopathy, that's really, I mean the next thing with the heart failure, a decrease in cardiac function. I mean, takotsubo you would assume, I mean it has sort of a classic presentation. It would sort of declare itself in a way with resolution. And we've seen that other cases where it's a little bit more persistence and then you do the standard guideline directed medical therapy for cardiomyopathy and hope that they improve. Now the, the insight from the group in Essen who's worked on this was that TNF alpha inhibition has, has helped. Now that's another, I don't want to go there. I mean, we've been there, patients with heart failure, shall we do those kind of therapies? And, but maybe this is different. So this is something where we need the basic science to guide us, the translational science to guide us. And so there's a lot at work in, in this area. The problem is

that these rodent models that are used, I mean that they're, they're, they're not perfect. I mean that they're really difficult. It's really difficult to create that same scenario in, in, in an experimental model so that we can, we can learn, but I think we're gonna be prepared to be creative, just like I've mentioned about abatacept and the JAK inhibitor in the future. I mean to, to maybe have new channels of therapies, but for the time being, it's whether it's the right thing or the best thing to do, I should say. We just give what we do, what we always do in these scenarios. But, but I think we'll, we'll, we'll need to see. And then going to the atherosclerosis, the coronary artery disease, that's a debated topic too. And so Tom Neland will tell you that, I mean, it is an important topic. We've seen that, I mean, after you start immune checkpoint inhibitor therapy, these cardiovascular events will really double if not triple and so forth. But we haven't seen it here that I have to be honest. I mean actually we've seen less than what you imagine. 'cause if you think about atherosclerosis, that's an inflammatory disease. You, you, you think given immune checkpoint inhibitor would be really oil into pouring oil into the fire. But I mean, we haven't seen mi mis left and right or strokes left and right. We just haven't. But this being said, there, there, there still might be a subset of patients who, who will experience this acceleration of atherosclerosis. So statins, I dose statins and he, in his, in the part report that they've published Tom Neil and his group statins seems to be be somewhat beneficial. Steroids, I mean, and you almost dealing like an arteritis, right? Like a vasculitis scenario. And, and there have been large vessel vasculitis reports as well, arteritis otitis. So I think calling your friend in the rheumatology department might also be something to consider and, and for some of these cases.

Dr. Sharonne Hayes: So for, I mean I, is it too much, is it too far to go to say that these folks with maybe cardiovascular risk factors that baseline are known? Should they all be on statins? Is there a role for aspirin? I mean it, it, it, where are we going in the future with either prevention of this from ever happening or, or or modifying the the, the risk?

Dr. Joerg Hermann: Yeah, I mean that's an excellent question. And again, I mean so debated, I mean 'cause it's really hard to pinpoint, there've been various risk factors postulated when you look at the ESC guidelines, we put in their cardiovascular risk factors. It's maybe more conceptual, hasn't been fully proven. Something women are, are at a higher risk. I mean, but I mean that's again, I mean maybe just one or two studies indicating that. But, but I would say cant hurt. I mean, I mean we're cardiologists. We love s statins. I mean I love s statins. I'm not taking one, but I love them and so have no disclosures either. But I think that definitely just makes sense. I mean, even apart from the, I mean that's often in cardio-oncology, the, the theme as well, apart from the cancer, cancer therapy. I mean if you have, I mean the setup, I mean it just makes sense to be on those drugs. Now aspirin we don't know as much now there's not only the arterial events. They also, there also is venous thromboembolism. And, and if you look at the, the oncology literature and guidelines, they do comment on this as as well. So immuno thrombosis the whole thing with inflammation and stimulating thrombosis. So that is a theme there too. So these patients that can have thrombotic events as well and they're prone more prone to it with the inflammation. So something to be aware of as well. Now preemptively, no one really does, does anything. I mean, I would say preemptively the oncologists hematologists don't even want to know about it, right? I mean they're just as like, I mean, how do we, how did it's, it's not so easy. I mean, how do we, and then again, back to the surveillance, I mean that's not commonly done where we're like, I

mean, and we can imagine this possible scope of it, right? I mean, how do you wanna preemptively or proactively monitor for any possible side effect with these drugs? I mean the cost effectiveness is, is just not there. And then I think, so it's just, I mean, healthy lifestyle recommendations, patients who meet the indications for those cardiovascular medications should be on them. And then how do we, I mean in terms of, I mean those who, who we need to see early on. Yeah, I think that's, that's, that's evolving. I mean at this end we're sort of in a reactive mode, but I think I agree with you. Ideally in the future, we'd like to be in a more proactive mode.

Dr. Sharonne Hayes: So my last question, should every patient who is started on one of these drugs be seen by someone like you in a cardio-oncology clinic? Or is this uncommon enough that, that it would be, you know, kind of a referral after the diagnosis? And, and I, I realize there's no right answer to this, but in today's world, what would you say to that?

Dr. Joerg Hermann: Yeah, so it's the volume question, right? So there was, and there might still be sharing legitimate concern that we don't have enough patients for all the trials that folks want to do with immune checkpoint inhibitors. And there was one estimate, I mean, how many patients in the US would be eligible for an immune checkpoint inhibitor? They're estimating maybe 50% of all cancer patients. So that is a huge number. And I mean, it's really expanding and it's, it's just not manageable. It's not practical to see everyone. And, but, but yeah, who do you want to see? And I think, so those are the ones who had cardiovascular events where sometimes these scenarios where patients had some recent decompensation of their heart failure where they have a cardiomyopathy to begin with. They had a recent mi they, I mean they have, I mean, some other setup for, for potential complication. I think those ones would be the ones to, to see where I feel like, and and other than that though it is, it is still, I mean more in reactive mode whenever, I mean they have, I mean these, these manifestations that that we get, that we get pulled in. And so I think that's for every, I mean general cardiologist, I think really what I said in, we said in the beginning, I mean we all need to be ready. I mean these drugs, if you think about 50% of all cancer patients in the, as potentially eligible, I mean, and then you, you, I mean even if you just have 1% of these millions of patients, I mean, we still have a lot to deal with.

Dr. Sharonne Hayes: We have a lot to learn. And obviously as the use of these drugs expands, we'll have a lot more, we'll get a lot more practice. And today you have really shared some very practical things, but also the extent to which we still don't know and shouldn't be dogmatic about treatment and diagnosis. And we all need to stay tuned. Is that right?

Dr. Joerg Hermann: Yep, yep. Absolutely. Stay tuned. And I mean, for those who are interested, we have a Mayo Cardio-Oncology CME course. It's in Arizona. Mayo Clinic Scottsdale is, is hosting it, if you will. And that's on November 7th this year. And so we'll be talking about immune checkpoint inhibitors and, and the adverse effects some more at that meeting.

Dr. Sharonne Hayes: Well, thanks for that plug, because I'm hoping those who you have piqued their interest, they will choose to, to join you in Arizona. Thank you so much. This wraps up this week's episode of Interview with the Experts. I'd like to thank Dr. Hermann for joining me today and discussing this really important topic.

Dr. Joerg Hermann: Thank you so much again. Yeah,

Dr. Sharonne Hayes: We look forward to you joining us again next week for another interview with the Expert. Be well.