Cardio-Oncology: What is the Big Picture, What Drugs to Use, and Tests to Follow

Dr. Sharonne Hayes: Welcome to the Mayo Clinic cardiovascular podcast series, interviews with the experts. I'm your host, Sharonne Hayes. I'm a non-invasive cardiologist and vice chair of faculty development and academic advancement for the Department of Cardiovascular Medicine here in Rochester, Minnesota. And today I'm joined by Dr. Chadi Ayoub, who is associate professor of medicine, medical director of the ECHO Program and, ACC, and a member of the ACC Cardio-Oncology Leadership Council. He also practices at Mayo Clinic in Phoenix. So today our topic is cardio-oncology, the big picture, what drugs to use, test to follow. With advances in cancer care, we're seeing more frequent cardiotoxic effects associated with many of these life-saving cancer therapies and dealing with immune checkpoint inhibitors in particular has become a specialty in and of itself. Today we'll discuss modalities that can be used to detect and evaluate cardiotoxicity as well as common adverse cardiac events associated with immune checkpoint inhibitors. And we'll review treatment options to prevent and address this cardiovascular toxicity. So welcome Chadi and, and glad you're here to share all of this with us.

Dr. Chadi Ayoub: Sharonne, thank you for the kind introduction and I'm really glad to speak to you today about this really important and growing field, which covers really an overlap of two important populations, cancer patients and cardiac care.

Dr. Sharonne Hayes: So can you first just share the primary chemotherapy agents that we as cardiologists really should be aware of that may cause cardiotoxicity? 'cause it's a growing list, right?

Dr. Chadi Ayoub: Absolutely. It's so rapidly expanding and can be hard to keep up with. And I should comment, the word cardiotoxicity is loosely applied. Most commonly it refers to LV systolic dysfunction or heart failure and agents that may cause this or worsen this. But it's really a very broad term that can cover many other potential side effects of cancer therapies, which could include, include accelerated coronary atherosclerosis, increase in cardiovascular risk factors, hypertension, treat, QT prolongation, arrhythmias, and of course with radiation therapy it can cause all of the above and and, and others. So cardiotoxicity is a loose term. The literature and the guidelines of which we have many guidelines now and there was, there was a complete LAC 10 years ago, but this field has moved so much. We have multiple guidelines. There can be slight variations in how they define cardiotoxicity, but if we're gonna use the most common and most concerning effect of cancer therapy on the heart, which is LV systolic dysfunction, that that'll be the main kind of definition for cardiotoxicity. There are a couple of acronyms I should comment about. The American societies would use CT ca cancer therapy, cardiac dysfunction, CTCD, whereas the Europeans will use a different term called cancer therapy related cardiovascular toxicity. The, the bottom line is we are talking about cardiotoxicity as you simply mentioned at the beginning, but just be aware there can be different definitions and terminologies referring to the same pain. And in concerning the, the main agents that can cause say LV systolic dysfunction. Most commonly the

initial group of medications was the anthracyclins, which we have learned a lot about and they're most commonly associated with the LV systolic dysfunction. And then the next most common group would be the HER2 targeted therapies spare initially in the breast cancer space with trastuzumab or herceptin and then pertuzumab and now others. But there's a wide array of other classes of cancer therapy related medications that can cause heart failure, LV systolic dysfunction. To touch briefly on these tyrosine kinase inhibitors, not all but some from the BCR able class nilotinib or erlotinib, it might be the two most prominent. Then there's the group of proteasome inhibitors of which CARFILZOMIB might be an example. And then not all VEGF inhibitors but sub, and I'm thinking sun may be top of my list would be associated with LV solid dysfunction in some patients who may be susceptible. So it's a long list. The European Society of Cardiology released a guideline just years ago and it's beautifully presented and they do present tables of the different classes. So for people feeling a little bit overwhelmed with which cancer therapy drug might affect my patient, that could be a, a useful resource to review as in which might be the more likely offenders

Dr. Sharonne Hayes: Because many of these patients obviously have been treated with multiple agents over sometimes many years and figuring out which one that gets us to figuring out. So I, if we're talking about LV dysfunction, obviously I'm thinking echo is the start, but it isn't the end for these patients. So tell us how we would go about diagnosing what, what is the surveillance or or diagnostic protocol?

Dr. Chadi Ayoub: That's such an important question and I like how you term it figuring out, and really in the cardio-oncology space, it's really about risk assessment and trying to figure out who's at more risk, what's recommended across the board for all cancer therapies before they come to cardiology. And even having that echo is history and examination. And this is perhaps a little bit more controversial, perhaps an ECG, just a plain old electrocardiogram to screen patients who might be at increased risk for developing potential cardio toxicities. Now patients who might be identified as having previous cardiac disease on that history and examination would warrant further examination with an echo. So it's not a one size fits all. Definitely for higher risk chemotherapies like Trastuzumab, and this is FDA mandated, they have to have a baseline echo and then an echo every three months during the course of therapy. And for anthracyclins, it's certainly recommended everyone have a baseline echo. And depending on the dose of anthracyclins, 'cause the dose of anthracycline is really associated with risk for developing OB systolic dysfunction, then the frequency of echo surveillance during anthracycline therapy can be tailored to that patient's risk. And then for some of those other potentially higher risk medications in cancer therapy that we discuss, whether they're chemotherapy or targeted immunotherapy, it really comes down to the patient's risk. If they're low risk, then they do not need an echo. But if they're high risk as in the patient has cardiovascular risk factors or cardiac symptoms or the medication they're receiving, the cancer therapy risk is high, or if they're receiving synergistic cancer therapies like radiation therapy and high risk cancer therapies, then definitely an echocardiogram at baseline is recommended. And this is consistent in all the different guidelines in this space. It's more personalizing the frequency of surveillance with echo, which is the frontline cardiac imaging modality to detect

cardiotoxicity. It's personalizing the frequency of that depending on the patient's risk and their cancer therapy and the risk of developing toxicity bed. And I'd be happy to share some examples. I mean we've talked about Herceptin and potentially anthracyclins, but for, for other spaces like immune checkpoint inhibitors that you've mentioned, you know, it's, it's debatable where the routine screening there is cost effective and a benefit to the patient. We have to think not just cost but burden of testing to the patient for a complication that more recent data is suggesting it's frequency is 1% perhaps not as frequent and therefore not subjecting patients to burden of additional testing in addition to their extensive cancer therapies and testing required there. So it really comes back to that figuring out on a patient level, what's their risk, what's their treatment and how do I tailor that surveillance?

Dr. Sharonne Hayes: Yeah, so say you suspect cardiotoxicity, there's signs and symptoms, maybe the echo is abnormal, what's the next step in terms of treating it? Because obviously it, it sometimes, and I've experienced this with my own patients, this was the one drug that was holding their cancer at bay and now they've had a cardiac complication and that's such a tough situation to be in.

Dr. Chadi Ayoub: Absolutely. And I think that that comment reflects kind of the title of this podcast, the big picture. And I think that's where we've learned more about kind of our role as cardiologists in the space of cancer therapy. And we've moved away from the question of, okay, there's an abnormality I'm testing, should I stop chemotherapy to the question now of how do I support the patient through the chemotherapy with this abnormality to give them this lifesaving treatment that may be first line for them and the second line may not be as effective and might actually worsen their survival and prognosis. So it's that, that comment is so important and shows how we've moved in this space and in this field it really comes down to the specific situation, the degree of impairment, the drug that's being used and what cannot be understated is this multidisciplinary approach where often it takes picking up the phone and talking to the oncologist. They are expert in cancer therapy and know what's first line, second line. In some cases there are actually viable second and third line alternatives that are had, you know, close efficacy to their current treatment, which has potentially cause cardiotoxicity and then that makes it an an an easy answer. In other cases, like the case you just described, this is really the best option for the patient. And let's take say the, the two most common offending drugs in in the cardio-oncology space with anthracyclins, the cardiotoxicity can be potentially irreversible and it depends on the ejection fraction drop. If the ejection fraction drop is say mild, we would not wanna withhold cancer therapy and that'll be the first comment to the oncologist. But we would wanna start what's called cardioprotective therapies. Now we have a lot of data in the established cardiology world for heart failure with reduced ejection fraction term GDMT or guideline directed medical therapy. And we have the pillars, the ACE inhibitors, sacubitril, Valsartan, Entresto in that category as well. The beta blockers, SGLT two inhibitors and the MRAs like spironolactone. These are the main medications used for cardioprotection. When we see a mild impairment in LV systolic dysfunction when a patient is receiving cancer therapy, however it's still controversial and the evidence is still early and limited for the application for cardio protection as opposed to treatment of more pronounced systolic

dysfunction like an ejection fraction drop below 40%. So if it's someone on an anthracycline and the ejection fraction has dropped to 50% or 45%, there's this concept now of permissive cardiotoxicity where we would say continue this lifesaving cancer therapy. But we'll screen the patient more closely with more frequent echos looking at both ejection fraction and this other marker on the echo called global longitudinal strain. And we will see if there's decline further despite initiating cardioprotective therapy, which in the cardio-oncology world definitely involves an ACE inhibitor and a beta blocker with more trials forthcoming about whether SGLT two inhibitors and statins and MRAs potentially may be helpful in cardioprotection for . But we would initiate these on a case by case basis and then watch the patient closely or trastuzumab, which is perhaps the other common medication that can cause drop in ejection fraction. This tends to be irreversible. And again it depends on the drop in ef, if it's in the 40th, so mild LV systolic dysfunction, 40 to 50%, we would have a discussion with the oncologist start these cardioprotective medications and watch the patient closely. But if the EF continues to drop below 40%, then we may have to discuss an interruption and talk about upper possibilities. And this approach can be extrapolated to other cancer therapies.

Dr. Sharonne Hayes: We hold our GDMT, you know the our, what we've always done is appropriate. I guess one question is, in some patients and there have been studies where when you start that anthracycline you actually start the ACE or ARB, is that standard or is that more individualized or not done anymore?

Dr. Chadi Ayoub: That's an excellent question and we often get these questions from some oncologists who are asking, what's the best thing to do my patient to be cardioprotective and to nip this in the bud before it happens? And the short answer is we do not routinely start these medications that are thought to be cardioprotective initially. It really comes back down to figuring it out for that patient, what's their risk? Even with the anthracycline of developing cardiotoxicity, if they have no cardiovascular risk factors, the EF is plum normal, it may actually be a disservice to indiscriminately start these medications on patients receiving chemotherapy. Because you have to remember, we all have to remember they they, they're nauseated, they anorexic, they dehydrated, their blood pressure is dropping and then we're studying these medications which we thought might be helpful, but actually they make the blood pressure worse, they feel lousy and they may not have been at risk developing cardiotoxicity to begin with. So it's a little bit more individualized and we use obviously echo and then strain this global longitudinal strain to screen for people where we can potentially pick up cardiotoxicity before the ejection fraction drops. And if there's abnormalities on this strain measurement on echo, then it may be reasonable to start maybe one or the other. That approach I think started 20 years ago when Dr. Al initially published in the doxorubicin cohort in breast cancer ACE inhibitors attenuated decline in EF drop in that 10% of patients at that time that were gonna develop it compared to people who weren't. But subsequent trials has shown actually the frequency of anthracycline mediated LV dysfunction has become less. And part of that is we are now wiser, we know high dose anthracyclins cause LV star dysfunction. So most oncologists don't give the higher dose unless they absolutely have to. And there's other mitigating techniques say bolus instead of an infusion liposomal doxorubicin instead of the other formulation and these

decrease the risk. So we've seen that starting ACE inhibitors in prospective trials have shown mixed or even negative results and that's a testament to how the field I think has moved and our populations have changed in terms of how we treat them.

Dr. Sharonne Hayes: All right. Let's switch gears just a little bit. So immune checkpoint inhibitors, icis it's revolution revolutionized the care of some cancers. Tell us about cardiac toxicities here. What have we learned from our own study of these patients?

Dr. Chadi Ayoub: Absolutely, and I always think of former president Jimmy Carter when we talk about revolutionize the care of some cancers. When I was in medical school, I was told metastatic melanoma as a death sentence and President Carter in his nineties developed metastatic melanoma to the brain and then he received an immune checkpoint inhibitor and was completely cured. So it's not an understatement to say revolutionized, they do cause multiple immunological adverse toxicities like myositis, like pneumonitis, like myasthenia gravis. And then the most feed has been myocarditis. And in more severe cases like fulminant myocarditis, which is inflammation of the heart, a high mortality rate has been described. We've learned more about immune checkpoint inhibitors as time has gone on. And we know that myocarditis now occurs in roughly 1% of patients receiving immune checkpoint inhibitors. And actually we've looked at our Mayo Clinic experience, we've looked at 5,000 patients who've received immune checkpoint up to 2022 at all three sites of Mayo Clinic. And our data suggests that the frequency of immune checkpoint inhibitor related myocarditis is about 1% and it occurs in the first four months after receiving immune checkpoint inhibitor therapy. And we've learned that most of the adverse events, it's not kind of, again, a one size fits all, it depends on how severe this myocarditis is. It could be milder on the spectrum where potentially stopping the immune checkpoint inhibitor, treating the inflammation with prednisone and potentially re-challenging is an option to fulminant myocarditis where there's hemodynamic instability, vtac or complete heart block and and the patients at severe risk. So it's a spectrum and we've learned more. ECHO is important, but patients with a normal ef, even with myocarditis or low ef, it doesn't really predict their mortality. We've learned that it a low EF at myocarditis predicts more heart failure but not mortality. But what we've learned is we need to take a more comprehensive approach because the presentation of myocarditis can be non-specific or dramatic, and we need to use all the tools in the toolbox. So echo MRIs invaluable, but again, for the sicker patients, they might not be able to tolerate a 45 minute examination and in a quarter to our patients, they were not actually well enough to go down and have an MRI. So it's, again, it's not a one size fits all, but awareness of this complication is so important.

Dr. Sharonne Hayes: And the treatment, if you've got somebody who's really sick is high dose steroids and stopping the treatment at least temporarily correctly. Or what else?

Dr. Chadi Ayoub: It's, it is high dose steroid. So IV methyl prednisone for the first three to five days and then a high dose steroid with a slow taper. It really helps if we have confirmed the diagnosis,

whether it's by MRI to get more confirmatory data, but it might be negative and that doesn't rule it out or biopsy if needed. But what we've learned is re-challenged with immune checkpoint inhibitors. So say we've treated them with the, the steroids, we withheld the immune checkpoint inhibitor. Of the 60 patients in our 5,000 roughly who had myocarditis six were rechallenged. And after their troponins had settled and the acute inflammatory process had been dealt with, and actually four of them did fine and two had to have the immune checkpoint inhibitor stopped for other reasons like nephritis or a rash. So it is feasible to restart immune checkpoint inhibitor if the patient has survived and support them through that initial myocarditis stage. We've looked at our experience at Mayo of additional therapies like immunoglobulin or bar globulin or abatacept, which is currently in trial and I know Dr. Herman's been part of that trial, but only about 10 of our 60 patients needed additional therapy on top of prednisone and the market there was much higher troponin instead of a mean troponin of 400, we're talking about a mean troponin of 900. So we're talking about sicker patients where they might be having arrhythmias and the the cardiologist and the, the multidisciplinary team is concerned we might be at higher risk of a catastrophic event and then need to add some on top of that steroid.

Dr. Sharonne Hayes: Well, it's good to know that we have some of these other agents and we look forward to your publication on this series coming out as well. Let's, let's switch gears just a little bit to some of our older treatments. Let's talk about radiation therapy in the heart. You know, I I, I remember when they really didn't target, you know, I would see patients in their fifties who'd had inflammatory breast cancer and they'd just been blasted and they had valve disease and coronary disease and myocardial disease and pericardial disease. And I know we do better, but it's still an issue. So what can we do to minimize radiation toxicity from a cardiology standpoint,

Dr. Chadi Ayoub: Again, that's such an important consideration. We've come such a long way in our understanding of radiation related heart disease when radiation is given, and we're talking about specifically breast cancers, lung cancers or esophageal cancers or thymic cancers, but extremely breast and lung where the hearts in the trajectory of those radiation and Hodgkin's, I should say Hodgkin's in the younger, in the younger group in particular, and that's probably top of the west. These patients have an inflammatory process as you've outlined, that encompasses the whole heart acutely. It's a pan carditis. We don't have a way initially of diagnosing that inflammation, but they come to us 10, 20 years down the line where that in initial inflammation triggered by that life-saving radiation therapy for the cancer has affected all aspects of the heart. It can cause valve disease, specifically the left-sided valve. And the telltale sign is that calcified aortic and mitral valve and intervalvular fibrosis on the echo, but can cause accelerated currently atherosclerosis and fibrosis within the myocardium and heart failure and constriction. Whole pericardium can be en case in calcium 10 to 20 years down the line. And it really comes down to risk factor in terms of modifiable as aspects from a cardiac perspective, risk factor modification, making sure all our patients who are gonna go and have radiation therapy have the hypertension hyperlipidemia fully addressed all how patients who are gonna get this therapy will have CT scans performed to stage their cancer. And it's such a useful tool for risk stratification from a cardiac perspective to pull up that non gated CT scan, change the setting to bone, which shows calcium is white more clearly, and

then scrolling down the heart and looking for calcium down the coronary tree. There's a lot of calcium and they're asymptomatic. It, it's like having a dedicated calcium score then a statin may be helpful, limited evidence for this, but it, it fits with our general approach in cardiology for risk factor modification. So that's what we could do risk factor modification, encourage that active lifestyle because there there's more patients that are gonna progress to that survivorship phase and then want to attenuate cardiovascular disease later. But then on the oncology side, there've been a whole bunch of new initiatives, like you said, we don't indiscriminately radiate the chest as we did in the days gone past with Hodgkin's. So we've got new techniques and that our radiation therapy colleagues implement more targeted radiation to the cancer that avoids the heart, shielding the heart where possible techniques like deep inspiratory breath hold where the chest is expanded and then say the target area is separated by distance from the heart. A little bit more simple technique but so effective. And now we have proton beam therapy. So Mayo Clinic Arizona was the first site to have proton B therapy instead of using X-rays, it uses positive ions, protons. And it's thought that these protons can target the cancer tissue with a little bit more precision and so cause less damage to surrounding tissues. And I know Rochester will be opening their proton B therapy in, in, in a year now. So there, there are developments in the radiation oncology space. However, I should note long-term data still needs to be established. We think this is a great initiative, but radiation heart disease turns up 10 to 20 years after the therapy. So we will probably have to wait that long to see our current initiatives both at risk factor modification and reducing the radiation burden to see how they bear at in the long term.

Dr. Sharonne Hayes: Any one liner about where you see the future of this field or of, of either treatment or management or prevention of cardiotoxicity as we save more patients with these important chemotherapeutic agents?

Dr. Chadi Ayoub: Absolutely. Personalized risk factor assessment is critical and that's the current state in, in cardio-oncology, assessing the patient's risk and the risk of the cancer and then using the tools we have at hand. That's my one liner for now for the future, I think, my goodness, it's such a rapidly expanding space. Artificial intelligence I think is gonna play a huge role in that risk factor and personalized medicine approach that might perhaps help us better screen patients. High risk and better understanding of genetics I think is gonna be a big player in the future as well. So I think we're gonna have even more tools than we have now at, at identifying these higher risk patients and intervening earlier.

Dr. Sharonne Hayes: Yeah, I, I think this whole thing we, we've talked a lot about the patient, but you know, patients who develop cancer often feel like they have lost all of their agency and being able to provide these therapies has been great, but including them obviously in these tough decisions because it's the values thing and it's quality of life that often we, we, we don't forget about, but we sometimes don't pull them in. And I think that's really been a big practice as we've had to talk to each other about this and talk to the patient. So thank you so much Chadi. This wraps up this

week's episode of interviews with the experts. I'd like to thank Dr. Ayoub for joining me today, today and discussing this important topic.

Dr. Chadi Ayoub: My pleasure. Thank you so much.

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