[MUSIC PLAYING]

KIRSTEN ROSE-FELKER: I'm going to focus mainly on our pediatric cancer survivors, rather than acute cardiotoxicities of pediatric cancer patients, because these are the ones that I'm going to see, but this is a prep for what's coming down the line for you. And hopefully, we can change some of this.

So I have no disclosures aside from the fact that I'm a pediatric cardiologist. And the objectives today are to review the patient and treatment-related cardiac risk factors facing our childhood cancer survivors as they enter adulthood, describe how our traditional surveillance practices have come about and how these may change over time, and how surveillance is determined, and who's ordering these surveillance modalities, and how we can reduce the risk of these patients as they enter adulthood.

So I'm going to start by saying that treatment-related cardiac death is not the second cause of mortality, but is the primary non-cancer-causing mortality in this population. In adult survivors of childhood malignancies, the rate of cardiac death is 10 times that of their siblings, and so this is really a population that we can affect.

The good news is that early detection of dysfunction, which we're starting now more and more in the pediatric population, can identify a high-risk subset entering adulthood and gives us a chance to intervene early. And if we can then follow the progress of our oncology colleagues in the pediatric survivor-- pediatric cancer survivor population, what used to be dismal mortality is now a greater than 80% mortality for all comers of childhood cancers. And you'll see in the next slide that more common pediatric cancers, like standard-risk ALL, now have a survivorship of greater than 90%.

And so we can follow suit and treat this population. So in 1975, just to rehash, there was a 61% five-year survival for childhood cancer, and in the current era, it's greater than 80%. There are over 500,000 childhood cancer survivors in the US, and that number continues to grow with every rewriting of the population statistics.

An estimated 60% of these patients have received or will receive anthracyclines as part of their treatment. And so that's the majority of what we'll focus on today is anthracyclines and radiation because, honestly, that's the best data that we have in our pediatric age group.

So that, at this point, you're probably tired of looking at the continuum of heart failure, but I think it's really important to see this graphically, because where cardiologists fall on the spectrum of this is often-- typically, it used to be, as patients were in stage C or stage D heart failure, where at least with anthracycline cardiotoxicity, the prognosis is dismal. And so the focus of our whole field is to move cardiology involvement up earlier.

So for our pediatric patients, often these patients are young, healthy kids with no other cardiovascular morbidities that are entering treatment. And so this is a great population not only to study, but also to affect. So the way that it works in our population-- we'll go more into this-- is that long-term follow-up typically begins usually at two or five years after patients have been in remission, when we consider them long-term survivors.

And we know, unfortunately, that we see a lot of patients at this group, and I think in the current era, with greater recognition of these toxicities, the cardiology consult is actually happening more closely to somewhere between stage B or stage C heart failure, where there is signs of cardiac changes on surveillance echocardiograms, or hoping to move that forward even.

So what are the risk factors for development in our pediatric population? I think the predominant risk factor is anthracycline chemotherapy. For our patients, as they enter adulthood, I think the difficult thing for an adult cardiologist is, it's sometimes hard to know what they got because it was at a different institution. They don't have a summary. They may not remember what they got, and so we'll talk a little bit about how you might be able to start sorting some of that out. But the typical places that we see high-dose anthracycline use are in aggressive solid tumors, and then aggressive blood tumors like AML.

Any patient who's had radiation therapy affecting the thorax, and that doesn't have to be direct mediastinal radiation, often radiation, as you know, reflected on the spine and other places can affect the heart. And I think traditionally we thought about 35 gray as being high risk, but more and more data is coming out to suggest that doses of 15 gray are considered clinically meaningful.

And we don't have many patients that start out with cardiovascular risk factors as children, but they definitely acquire them over time. And the patients that are treated at a young age, particularly our kids that are treated in infancy and toddlerhood, when the myocardium is particularly vulnerable, are at high risk.

So just to review-- and I'm not going to spend much time on this-- the mechanism of anthracycline toxicity, I really like this graphic. So anthracyclines bind to topoisomerase IIB in the cardiomyocyte, which causes disruption of DNA double strands and causes mitochondrial dysfunction.

Additionally, this causes a production of reactive oxygen species, which directly damage the myocardial and mitochondrial membrane and start to activate cell-death signals. There's also some disruption of cardiomyocyte pro-survival pathways that are being more and more elucidated.

And anthracycline cardiomyopathy, I think this picture is really important, and if you can burn it into your brain, it may help when you talk to pediatric cancer survivors. This is a micrograph of a patient who was treated with-- or, actually, two different patients, where doxorubicin is seen.

In the picture on the left, you can see the doxorubicin accumulating in the cardiomyocyte, and I think the picture to the right are cervical cells. But the reason why I show this is because patients will remember the red chemo. And if you ask them if they ever got the red chemo-- and some patients will call it the red devil-- then they'll almost always remember that, or you can have them call their parents. Their parents will surely remember that because they're counseled at the time of getting it that this has cardiac side effects.

We know at the tissue level that doxorubicin and other anthracyclines are dose-dependent, but there's a lot at the organ level that we're still working to understand because we see some pediatric cancer survivors that have been exposed to very high doses that really have not had any significant change in their echo function many years out, even though that's probably not the norm.

Definitely, cardiac reserve at the time of administration, and I mentioned our younger survivors, or our younger patients, are at higher risk, and if there's coexistent damage from radiation, and additionally, a lot of information about genetic variability that is being studied.

This is the known dose-dependency of anthracycline cardiotoxicity, as-- the typical rule that we use is 250 milligrams per meter squared, representing the highest dose for developing a congestive heart failure. Although, as I mentioned, there's really no safe dose, and so you'll see from some of the surveillance guidelines that any anthracycline alone will mandate some cardiac surveillance going forward.

So how do we see this come up? In the pediatric population, acute cardiotoxicity, I think, is what we see less commonly, although, if I see patients with true heart disease, often this is what I see. This is in the setting of acute or immediately following anthracycline administration, typically, changes in left ventricular function that are seen on echo.

Kids have a very good tolerance for a change in ejection fraction, and so many times, this is picked up on surveillance imaging and is not associated with symptoms, but it can also be arrhythmia and conduction abnormalities. And this is the one that, if we start ACE inhibitors and beta blockers in this population, these are the ones that are most likely to improve and have a better prognosis, at least in the near term.

The chronic dose-related cardiotoxicity are the patients that will become part of the adult follow-up period, and this is much more common and, unfortunately, less responsive to therapy. Those that do have acute cardiotoxicity during childhood, that's considered a risk factor for the development of late cardiotoxicity, so we watch them. And that can manifest years after, as a matter of fact. As patients start to accumulate more traditional risk factors like hypertension and diabetes throughout their lifetime, these risks go up.

Radiation toxicity, we know, causes pro-inflammatory cytokines and results in [INAUDIBLE] and intimal proliferation, which causes narrowing of vessels and other effects such as fibrosis, which can affect the valves and pericardium.

And so how do we determine surveillance in the pediatric population? Any patient who's going to receive a cardiotoxic therapy will get an echocardiogram at the onset of therapy as a baseline. And then the individual treatment protocol will dictate how often an echocardiogram is done between infusions and between cycles of their chemotherapy.

And then following treatment, their surveillance is going to be according to the Children's Oncology Group protocol, and I'll go over this with you because it's really easy to find. Every oncologist should be using this protocol. Unfortunately, not every patient follows up with the recommendation, but if we use this, I think we can avoid a lot of these problems in the future.

So I would add this to your web browser of, this is a population of patients you see. The Survivorship Guidelines have a ton of information, both patient handouts, as well as guidelines for physicians. And there's a slide here that is very busy, and I'll simplify in further slides, but this looks at anthracycline chemotherapy and goes through the therapeutic exposure late effects and what is recommended of providers afterwards.

So you can see here that the frequency of echo is dependent on the anthracycline dose here. If patients receive any dose of anthracycline, they should be getting a minimum echo every five years going forward for indefinitely to monitor their cardiac function because, even more than patients with congestive heart failure, we follow many more patients with asymptomatic decline in function.

So quickly, it's been touched on, the doxorubicin isotoxic equivalent dose. That's what an oncologist is going to be using to determine the echo frequency. And, basically, the major take-home from that is that anthracyclines are not equipotent gram for gram. Some of them are much more toxic than others, and this calculation should take that into account.

And you want to include all doses administered over a lifetime. It's important to know if a patient relapsed and had another cancer that was treated and how that was treated. And we calculate it according to their body surface area at the time of treatment.

In terms of radiation therapy, this is all in that Children's Oncology Group guideline. This goes through heart radiation fields and fields that sometimes have reflective radiation to the heart. It's important to know the mean dose of radiation, and I think it's pretty universal that this information can be more difficult to find in the medical record.

But the mean dose and the percentage of the heart volume receiving the dose, there are a lot of efforts towards getting this to be a little bit easier for other clinicians to interpret going forward, especially with this field of cardio-oncology. And so I'm hoping that gets easier with time. And there's an increased risk, of course, with concomitant use of anthracyclines-- just like with anthracyclines, younger age at exposure and any patient with underlying structural disease.

Just like the slide for chemotherapy, there's a slide for radiation, and that really depends, for radiation therapy, on whether or not the patient received anthracyclines. I wonder if this will change as more and more information comes forward about radiation therapy, but, basically, if you have greater than 35 gray of radiation therapy, which is considered the higher dose, then you'll have the highest frequency of echo screening.

So this is the chart. This is the-- really, the take-home point that the oncologists are using to determine surveillance. The most important thing to note is that it's easy to find one. And then there's some additional surveillance that is not on this chart, and those are in women that are considering pregnancy or who are newly pregnant.

So in these women, it's really important to remember that if they've received any dose of anthracyclines and radiation or high-dose anthracyclines or high-dose radiation therapy, that they should have an echo at the beginning of pregnancy and throughout their pregnancy because of their increased risk for peripartum cardiomyopathy, especially if they have a history of dysfunction.

And so I think an important thing to realize is that, in the current era, these echocardiograms are typically ordered by an oncologist, and they're communicated to a patient by an oncologist, and they're understood by an oncologist. And I think in my communication with oncology colleagues, it's been a really great experience because I've learned a lot from them. And I've also been able to teach them that an echo gives a lot more information than just an ejection fraction, and that these subtle differences in echo over time, especially looking at the actual images rather than just the report, can really tell you a lot about what's going on with that patient.

And we have a universal protocol at Children's, and we encourage our survivorship patients to have their echoes done routinely at Children's. I think that's a change that's happened in the past year, where patients were getting their echoes at satellite locations, and we couldn't compare image to image. Now they're being done with a universal protocol, which includes strain imaging and tissue Doppler.

So just before I get into the nice part of the conversation about how we can modify all of this, I just want to remind you of a couple of things. As these children age, what happens to them in terms of their other modifiable risk factors?

We know from the Childhood Cancer Survivor Study, which is a huge cohort study that has followed cancer survivors since 1970 and compared them to siblings-- there's over 27 centers in the US and Canada that are involved in this-- the survivors are twice as likely as their siblings to have hypertension, diabetes, even after adjusting for BMI and age, one and a half times as likely to have dyslipidemia.

They're significantly less likely to meet guidelines for physical activity, and I find a lot in survivors that we tend-- I think families and survivors tend to protect themselves and think of themselves as sickly kids. And so we spend a lot of time trying to change their mindset and really encourage physical activity. And we know that these factors are more than additive to their cardiac risk with anthracyclines and radiation.

So what can we do? Starting with the oncology community, improving survival is the most important thing, which they've already done, but I think it's taking some of these patients off of this spectrum of heart failure and really stopping them after cancer treatment from coming any further along. And so they've already been doing this.

And in terms of primary prevention, there's been reduction in the lifetime cumulative dose-- oncologists have used less cardiotoxic derivatives, and we mentioned that some anthracyclines are more toxic than others-- alternative administration schedules, and then I think most importantly-- I have a slide next on dexrazoxane.

So in our center, we use dexrazoxane in-- as long as it's available, which was mentioned before that it-- sometimes has-- it's difficult to get. But as long as it's clinically available, every patient at UPMC Children's gets dexrazoxane with anthracyclines. If there's a shortage, it backs to patients that are receiving either high-dose anthracycline therapy or concomitant radiation therapy. But this is something that I'm hoping parents will remember and patients will remember to protect themselves going forward.

And then also, improvements in radiation therapy over time, like intensity-modulated radiotherapy and using smaller gates to define where the radiation is affecting.

So looking at dexrazoxane, I think this is also a really important image to remember because it highlights how anthracyclines affect a different receptor in cardiomyocytes than they do in cancer cells. And the reason why I show this is because there had been a lot of hesitation in using this agent, with some initial studies suggesting that maybe there was increased rate of relapse or secondary malignancies, which has since been no longer proven to be the case.

So dexrazoxane prevents topoisomerase II from binding to anthracycline in the cardiomyocyte and prevents that complex from forming, which then would result in cardiotoxicity. Remember, in cancer cells, it binds to topoisomerase II alpha rather than II beta, so it doesn't affect the efficacy of anthracyclines at all. There's also a thought that there is some component of decreasing and mopping up oxygen-free radicals, and it's been shown to significantly decrease the risk of heart failure during and shortly after therapy with anthracyclines.

Like I mentioned, there were some concerns initially about an increased risk of relapse, but several other studies have shown no interference with anti-tumor efficacy. And now the guidelines are to use this agent in high doses of anthracyclines.

So what can we do as pediatric cardiologists and adult cardiologists? We talked about being happy now that maybe the cardiology consult has moved up a little bit. I think our goal is to just move that cardiology consult up even further, and so that we're involved in the surveillance of patients who are at risk, because I think we are still missing-- by the time we start to see a change in their function, we're really missing an opportunity to treat them.

And so what we do in our clinic is really we meet frequently with our survivorship oncology team. We do a lot of talking about preventable risk factors, maintaining healthy body weight, trying to get more regular physical exercise, starting to track lipid abnormalities earlier, during childhood, and making sure blood pressure is well controlled.

We also have been trying to assist patients with transitioning to a cardio-oncology team because the old paradigm was for patients to move and have their-- all of their survivorship care be managed by their PCP, and that, I think, decentralizes some of their care, so trying to at least make sure they have someone to check in with if their echo changes.

So there's a great statement from the American Heart Association on reducing cardiovascular risk in pediatric patients, and this is something that all of you do on a daily basis. But there are three breakdowns in terms of our cancer survivorship population that are important here.

Stem cell transplant recipients are considered the highest risk group, and often in the pediatric age group, that group has received cancer therapy prior to becoming-- prior to going on this stem cell transplant. Chest irradiation is considered a moderate risk, and cardiotoxic chemotherapy is considered at risk. And this is an important guideline that I use every day because it gives me information on where to target our blood pressure and lipid goals depending on their level of risk in the pediatric population.

For example, if we have a stem cell survivor with hypertension, we're not going to give them a while to wait and see if lifestyle modifications would help, like we would in other kids. And this is-- there's a lot of really helpful graphics in there, like this one, that take a little while to become familiar with them.

So then lastly, secondary cardio protection, unfortunately, we don't have a lot of great data in the pediatric clinical research tools that we have, to really show that using these medicines in a preemptive way before there's any changes on echocardiogram is helpful, although there are ongoing studies. And a lot of adult studies are suggesting that this may not be the case, as you heard of this morning.

Our practice right now is to use ACE inhibitors and beta blockers in patients who've had some asymptomatic change in their surveillance echo. I think the move after the PREVENT-HF study, which is a prospective study using low-dose carvedilol in patients at risk for developing cardiotoxicity, may change how we do that.

So I think the take-home points for today are to remember that surveillance echocardiogram in pediatric survivors is lifelong, as a minimum of every five years for any patient who received anthracyclines or over 15 gray of radiation, that we need closer monitoring during pregnancy, given the increased metabolic demand of that time, that we would recommend referral for those even with asymptomatic changes in their echo, and that we should regularly assess our survivors for other cardiac risk factors and manage those.

And so we have a Survivorship Clinic at Children's and a cardio-oncology clinic that happens at the same day. Dr. Tersak, if you haven't met her, is wonderful, and she's the director of the Oncology Survivorship Program and is a wonderful source of information and education, as well as referrals. And then, I have a clinic that happens at the same time that we're seeing patients. Again, thank you for the opportunity to talk and teach.

[APPLAUSE]