SPEAKER: We're very lucky this morning to have Dr. Sahni here with us today. Quick intro, Dr. Sandy completed medical school at the Jayan Medical College in India. She went on to complete her internal medicine training at Long Island College Hospital in Brooklyn. Then she went on to Beth Israel, where she did a cardiology fellowship.

Before joining Mt. Sinai, she was the CCU director at Metropolitan Hospital. Currently, she serves as an associate professor here at Mount Sinai. She is the director of the cardiology consult service, and in 2013 established the first ever cardio oncology clinic here in the Mount Sinai Health System.

Dr. Sanhi's cardio oncology clinic sees over 3,000 patients annually, from all over the tri-state area. In addition to her clinical interest, Dr. Sanhi is a phenomenal clinical educator, and is a regular favorite amongst the house staff on the teaching service. Please join me in giving a warm welcome to Dr. Sahni.

[APPLAUSE]

GAGAN SAHNI: Thank you. And I'm sorry I was stuck behind a garbage truck. But besides my disclosures, which are none, a disclaimer that the next 45 minutes or so are going to be a roller coaster ride of a lot of information that you probably have never heard before.

But that's why you have me as your seat belt. So we're going to quickly divide the talk to an order for simplification. We're going to try to understand what cardio toxicity means. What we can do to early detect, prevent, and treat it.

Beyond cardiomyopathy and CHF, or the other cardiotoxicity, we will quickly touch on that. A little word on radiation-induced heart disease, some little bit stuff on bone marrow if you have time. And a few nice videos on oncological emergencies.

So let's start with a horrible sting math. Since we're all awake, we haven't had our coffee in the morning, let me wake you up with a little bit of math. And the math is kind of like a sweet, sour kind of potpourri.

In the sense that in 2016, we had 15 and a half million cancer survivors. And that's thanks to our wonderful oncology colleagues, and the strides that we made in the oncological world. And luckily, 70% of these people who've beaten cancer are all going to live for five years or more.

Yay. But here's the bad news. And the bad news is that you beat cancer, and if you are above the age of 50, and you're a man, there's a 50% chance, and if you're a woman, there's a 40% chance that you beat cancer. But then you're going to have to deal with some cardiovascular disease in your lifetime.

And not just this. Our kids, our kids who are beating cancer are growing up and they're going to be our adult patients. And luckily, 80% of the children who have beaten childhood cancer are going to become adult survivors. And as of 2013, the last data that we have, about 420,000 of these kids basically are going into adulthood and are cancer survivors.

And by 2020, next year, they're going to be half a million of these. And as for the Childhood Cancer Survivor Study, it's a pretty dismal story for these kids. I mean, not only have they gone through the horror of childhood cancer. But they're going to have a 7-fold higher tumor mortality, and a 15-time more chance of developing cardiomyopathy or CHF in their remaining lifespan.

So this bit is dismal. And the third reason why I want to dwell on the math of it, and why cardio oncology is such an up and coming field, is that so far we've done a pretty shoddy job of it. And this is actually a 2000 study coming out of Stanford. There's not a community institution.

It's coming out of Stanford, where they took about 88 patients who were receiving some kind of breast cancer therapy, either anthracyclines or trastuzumab. And guess what? They started off with a baseline EF of about 60%, which as you know is normal.

And 40% of these people, after they had completed the therapies with anthracyclines, Herceptin or both, ended up having a decline in LVF to less than 55%. But guess what the bad number is? Only 40% of these people were put on an ACE and a better than RB.

Half of them only were put on a beta blocker, and only half of them ever saw a cardiologist. So this is a pretty shoddy job. And this is not like, you know, early 2000s. This was less than a decade ago.

And so that's why I want to take you back through the math of cardio oncology, and ancient history. And unfortunately, or fortunately for you guys in this room, there's a lot of data to go through, right? So I'm going to start with a flashback to the 1960s, when these beautiful, by the way, my photograph of the Adriatic Sea.

Where basically we discovered streptomyces peuctius. A little bit before my time, but hey, in 1960s, the streptomyces peuctius was isolated, from it was isolated Adriablastina. Which was initially thought to be an antibiotic, right?

But hey, we discovered it for its oncological properties. And it was initially named adriamycin because we thought it was going to have antibiotic properties. Turned out to be an oncological drug. And so remember, mycins are antibiotics.

So we renamed it Doxorubicin, because it's not on antibiotics, an anti neoplastic agent. And that's where our oncological journey started first. And so, fast forward a couple of decades. We used anthracyclines for breast cancer, a lot of solid tumors.

And we used it beautifully. We saved people from cancer. We use it indiscriminantly. We use low doses, high doses. And we saw this data from Vonhoff et al, and he started observing. And remember, this is pre-echo data. So these are people presenting with clinical heart failure.

Florid heart failure, right? So he started noticing that hey, the higher the doses I give of anthracyclines, these people are developing heart failure, clinical heart failure. And in the 1970s, he thought the cutoff number was 550 milligrams per meter squared.

He said, if I bombard them with more than just 550 magic number, they are going to develop heart failure. So let's try to limit to lower doses, yeah? Fast forward a couple of decades more, and this is data out of MD Anderson et al.

And this is not 550 milligrams per meter squared. We're starting to see cardiotoxicity, now this is echo era, be more vigilant. They're more aware of the cardiac toxicity of adriamycin, or Doxorubicin.

And they start saying, well, you know what the cut number number is probably 450 milligrams per meter squared. It has a cumulative dose. If you bombard people with more than that, they're developing heart failure. And meanwhile, we had the luxury of cardiac biopsying these people.

We did something very little on cardio oncology now. But hey, this was when echo was just emerging, et cetera. So in the 1970s, 2000, we took these people who we thought were developing cardiac toxicity, we took them to the lab. And we did cardiac biopsies on them.

And if this is the normal sarcomeres in the heart, we started seeing big time alveolar disruption. The cells were dying. There was line out apoptosis. Cells were dying. So it's not dysfunction. This was not stunning. This is not mitochondrial dysfunction.

The cells were just devastated against them, under the microscope. And not just that, we started seeing the hey, not even the 450 or the 550 magic number, we were seeing these biopsy changes in lower doses, as low as 300 milligrams per meter squared.

And we noticed, we were able to risk stratify, and see well, you know what? The people who were getting had more risk factors, had got combination chemotherapy, got radiation. These people were showing worse biopsy grades. And not all anthracyclines are the same.

Some are probably less bad, compared to adriamycin. And we came up with a definition of type 1, and type 2 cardio toxicity from it. So here are the next, about, half a dozen slides are going to be about different mechanisms of cardio toxicity.

And what is this type 1, and type 2? And this is a dated question. And again, I'm one of the people who makes questions for medicine cardiology boards, so I'm not going to defame my type. But this question is a very popular one in both cardiology and medicine boards.

And they're still stuck on it. And I'll show you why it's not right to be stuck on type 1 and type 2. But this really emerges from the earlier anthracycline studies, based on these biopsy studies. And type 1 and type 2 cardio toxicity, if you really have to take home, is type 1 is a bad guy.

Type 2 is a not so bad guy. So type 1 is what doxorubicin induces, the horrible slide I just showed you before. Where the findings on the biopsy is outright vacuolations, sarcomere depression, necrosis, cell death, apoptosis, right?

And more importantly, it is cumulative dose related. Higher the dose you give them, the worse it's going to be, the apoptosis. And it is irreversible. Worse is, hey we took patients with other cardiotoxic drugs, just trastuzumab, put them under the microscope as well.

And this is a little nicer guy, the type 2 cardio toxicity. Which a, causes mild site dysfunction, and we put them under the slide. We do not see that horrible vascular disruption. It is not dose-related, which means you can give cumulative doses. And it does not-- it is basically reversible, and a much better prognosis.

So these are the three major differences between type 1 and type 2 cardio toxicity. You really have to take home a board question today. OK? So as I said, the dose-related cardio toxicity of anthracyclines is so magnificently related to its dose that there's probably a 50% chance, or a patient come to me, say what is my chance of developing cardiomyopathy?

It's a hard one to answer. Hopefully, in today's day and age, we're not bombarding anybody with 700 milligrams per meter squared, assuring a 50% chance of cell death. But we try to limit them to lower doses. And of course, remember this is cumulative dose.

So if you had a child that survived lymphoma and was giving anthracyclines as a child, and God forbid developed breast cancer later on, or sarcoma. And you bombarded him with second dose of doxorubicin, remember that clock started as a trial.

So they've already received say 250 milligrams per meter squared, and you're giving them another 250. That's 500 cumulative exposure, so they will fall into this category, which means I have a 25% chance of developing cardiomyopathy. And not all anthracyclines are equity-- we know this not from clinical studies, from biopsy studies as well.

So if we take doxorubicin to be the big daddy of cardio toxicity, at bolus doses of 100% cardio toxins, say doxorubicin is probably 3/4 as bad in similar oncological doses. Idarubicin is probably the best, and in a lot of my leukemia, lymphona patients with cardiomyopathy, I'll have a conversation with my oncology colleagues and say hey, the oncological benefit of idarubicin is a little bit better.

You really need an anthracycline regimen. This is probably a better choice. Epirubicin is also less than compared to doxorubicin. And the way in which you infuse the anthracycline also makes a difference in the cardio toxicity. Now, horrible busy, basic science slide.

But stick with me through this. And the mechanism is important. Because if we're going to talk about prevention and treatment, we need to know how this drug kills the cells. And so for the longest time, we thought with the two theories on the slide, so let's go with the old guy, old theory first.

So we for the longest time thought that doxorubicin combines with the ferismoiety and becomes this doxoferismoiety which is able to penetrate the cell membranes and get inside the cardiac sarcomere. It's able to lipid peroxidate inside the cell. And here, it's able to generate this horrible compound called doxisemiquinone, which is basically responsible for the radical oxygen species.

And it basically leads to mitochondrial disruption. It goes it disrupts the NOS pathway, affects a contractile of practice. Affects the sarcoplamic reticulum. All this is from this bad guy called doxisemiquinone, and so we thought, hey, if we prevent doxo from attaching to ferismoiety, or take away or chelate this ferismoiety from the doxu.

Hey, it can't enter the cell. And even if it does, it's not going to generate the semiquinone molecule. And hey, we can stop the destruction of this cardio toxicity. However, and we know from animal models as well as interventions that more of the cardio toxicity is through this guide called topo 2B.

Now, there are two kinds of topoisomerase molecules in our bodies. There's topo 2A, which is present in cancer cells. And this is what the anthracycline, the doxorubicin goes and sucks to, and kills the cancer cells. We need the topo 2A action.

Unfortunately, it's a topo 2B action, which is the bad part of it, because topo 2B is present in our hearts. And its present in our hearts normally. It's needed for like, you know, MRA, unfolding et cetera, normal replication, synthesis, et cetera. But the problem becomes when topo 2B attaches to doxo.

That's when all this bad stuff happens. And we know, to simplify the slide, this beautiful molecule is a topo 2B, which is present normally in our cells, like cardiac myocites. It's required for normal transcription and replication. Right? The normal stuff that we need for cell turnover and repair.

But when it attaches to our bad guy anthracycline, then it runs amok. Then it starts basically, resulting in DNA doubles strand and break. It activates the reactive oxygen species, mitochondria dysfunction. And leads to cell apoptosis.

So if somehow we can prevent anthracyclines clones from attaching to topo 2B, and let it to do its normal job, and not the disruptive job, well we can probably interrupt this cardio toxicity cycle. And that's what this drug called dexrazoxane zone does, which technically is an inoculator.

And we earlier thought that that inoculation model was why it was disrupting cardio toxicity. But when now we know from animal studies, and by measuring topo 2B levels in patients with cardio toxicity, that dexrazoxane disrupts this unholy matrimony between adriamycin and topo 2B, and interrupts the cardio toxicity.

So maybe future research, ongoing research, that maybe some people have more topo 2B in their hearts, and maybe are most susceptible cardio toxicity, and hence might benefit from prophylactic dexrazoxane. How does trastuzumab, the type 2 agent act, right?

Remember the slide where I showed you is a good guy, where it doesn't cause a vascular disruption? Well, it's a slightly less bad guy. And it becomes a bad guy only when it's in bad company. And that bad company is anthracycline. So let me walk you through the slide that hey, I bombarded somebody's heart with anthracyclines.

It started degenerating and oxidative damage, all that horrible slide that I showed you. And opaapoptosis necrosis starts to happen. Well, you know what? A heart has regenerative and repair mechanisms. And these happen through something called HER2 upregulation, which helps in the repair mechanisms of her heart. All good news, which means not everybody develops cardiotoxicity.

And even if they do our, the heart does have some repair mechanism in place. The problem becomes if somebody who's been pre-treated with anthracyclines and is starting to undergo subclinical or clinically apoptosis necrosis, and I bombard them, or rather my oncology colleagues bombard them now with trastuzumab, in that case, remember trastuzumab is a HER2 receptor blocker, right?

So my heart is full of HER2 receptors trying to regenerate itself from anthracyclines and I went and double whammied it with trastuzumab. And there goes my HER2 upregulation repair mechanisms. So it's not that the trastuzumab is killing the heart cells, or causing cell dysfunction.

It is-- we've seen not just in animal models. But we've seen in clinical trials with new adjuvant therapy that trastuzumab-induced cardiomyopathy is less than 1% to 3%. But it's hearts that were pre-treated with anthracycline, and have started the apoptosis necrosis, and were HER2 upregulated. These are the hearts that basically are susceptible to trastuzumab.

And the gamut doesn't run doesn't end there, right? So going beyond the anthracyclines, we have a whole slew. And again, as I said, it's a roller coaster ride. Do not obsess and start taking down stuff. My slides are available to you guys. I'm available to you guys.

So don't get into the system of, oh my god, I have to remember the 500 drugs that cause cardiomyopathy. But I just want to put these slides out there, just to alert you to the fact that it's beyond trastuzumab and anthracycline stories today. And I will take you through that roller coaster ride.

And how do we define cardiotoxicity or drugs causing heart failure? Well, we have a clear definition. And again, there's a lot of bickering between different societies, I'll show you the bickering as well. But as of 2014, the American Society of Echocardiography, since we use echo as a baseline of calling somebody that's having heart failure from chemotherapy defines fancy term, CTRCD, which basically means cancer therapeutics related cardiac dysfunction.

Because cardiotoxicity is too broad a term. Cardiotoxicity could be hypertension, QT prolongation, thromboembolism. So let's just stick to the heart failure component first . And so CTRCD, now this is important. And again, it's a definition that you should remember, needs two things.

First of all, your LVEF with chemotherapy should decline by more than 10% points over the patient's baseline. And it has to decline to a value which is below the lower limit of normal for your lab. So our lab, as you know, uses 55% as a cutoff for normal.

So if somebody's EF was say, 75, and now the next echo, say, is 65. And I'll come to that, that's not cardiotoxicity. Because the EF is still above 55. So you have to have A, decline by more than 10% to a value of less than 55%, or the value of your lower limit enamored for your valve.

And so pretty much the Mayo Clinic, ESMO, ASE have a similar guideline. So let's start with the bad guy, type 1, or anthracycline toxicity. So your initial evaluation, everybody gets an echo, OK? Everybody gets an echo. And so Mayo Clinic uses 50% as a cut off of their normal. So say 50, 55, whatever your lab is.

And so you start with a normal echo. You start anthracycline therapy. Now remember, this is dose-related, type 1. So for every increase that you exceed beyond 300 milligrams meter squared, remember we got that from the biopsy data from Billingham et al. We need to reassess the LVEF with the repeat echo.

So every time you dose escalate by 50 milligrams per meter squared above 300, we reassess with a repeat echo. And if the definition of CTRCD, if the EF declines by more than 10% to a value less than 50, or 55 as the case might be, you stop the drug.

Remember, this is irreversible. It's cell death. You stop the drug. If however, your EF was bad to start with, now that's a whole different ballgame. And again, I don't completely agree with this. Nothing is set in stone. OK? If a patient has six months to live without an anthracycline-based chemotherapy, this is a conversation I have with my oncologist colleagues.

The people that are we going to do this? Are we going to prolong life by six months, or six years? Or are we going to kill them in the next one month? So this is a risk-benefit tailor make thing that you have to do. Versus trastuzumab, where remember, this is type 2, a little bit better cardiotoxicity. Everybody gets a echo at baseline.

You start trastuzumab. Now here, as for the FDA guidelines, and from our studies of neoadjuvant trials, you reassess the LVEF every three months. So everyone gets an echo baseline. And every three months, and using trastuzumab for HER2 positive breast cancers, et cetera, run for about a year.

So you get an accurate baseline, and every three months. And here's where there is a little bit of a difference, if your LVEF declines by more than 10%, and a little bit of leeway. Because remember, this is dysfunction and reversible. So we have a leeway instead of 50%, we let them go down to 40%, if need be.

And if they develop heart failure, or declining LVEF, here is the difference, again. You discontinue it temporarily. Start your ACE inhibitors, beta blockers, cardio protective therapy. You repeat an echo in four weeks. And if the LVEF has improved, which it should if it's dysfunction, you can re-challenge the trastuzumab.

So that's the difference being anthracycline monitoring algorithms, and trastuzumab of type 2 cardiotoxicity. Difference is dose-related, the frequency of echo monitoring. And the fact that you can or cannot re-challenge them. Remember, nothing's set in stone, however right?

So this is historical classification, type 1, type 2. After having hammered this into you, the definition and the fact that it might come in your boards, I'm already fast forwarding to the iPhone XS. OK?

We have left this behind, and I can't even tell you how many mechanisms they are beyond anthracyclines and trastuzumab of cardiotoxicity. And let's leave type 1 and type 2 behind. And I'm not going to, don't worry, it's not a horror story.

I'm not going to go through the different mechanisms. I'm just going to touch a little bit, just to give you a little flavor of how not one size fits all approach can help in this. Right? So cyclophosphamide has this intermediary which is cardiotoxicity called acrolein, which goes through endothelial capillary damage.

And lots of new emerging curbs, and piperine, cucuremine to disrupt acrolein, and prevent cytoxin cardiomyopathy. TKIs, the tyrosine kinase inhibitors are vascular cardiotoxic drugs, as I call them. And they mainly act to VEGF inhibition, which basically makes them go into horrible basal spasm, which explains the amount of hypertension that these people have.

They get very thrombotic, again, through VEGF inhibition. They basically inhibit that PTGRF, which causes CHF. So a completely different mechanism, right? Touching a little bit on new kids on the block, which you may or may not have heard of until you're floating around on the 11th floor.

And this is where I come in. And this is one of our colleagues who is an exposition at Sinai. He was a 75-year-old doctor who had non-small cell cancer. And he was treated with this drug. And the reason why I'm saying is that you may or may not have heard of these new kids on the block. This drug called pembrolizumab, OK?

And he comes in with sudden shortness of breath. Remember, he has metastatic lung cancer. And so he comes into the ER, very short of breath. We thinking BE, CED, lung cancer. What is it? Troponin is 36. Horrible T-wave inversions of his EKG.

First thing, of course, you rule out PE. No PE. And then the CT shows that the lung nodules are the same as before. So hey, no progression of disease, either. We end up cathing it. Cathing, normal coronaries. And his echo, which was normal like a few months ago, when I'd seen him, was normal.

And now he has this new decline in LVF to 35% with a troponin of 36. And as we're doing the echo, he goes into complete heart block, and we transfer him to the CCU. What is this drug pembrolizumab? It's a designer drug, because our ex-president Jimmy Carter got it.

And it saved him. He's still around from his brain cancer, thanks to this fabulous designer drug. And really, I'm not belittling it by calling a designer drug. It is literally a lifesaver for so many metastatic and lymphatic malignancies. And here is where I'm going to show you, again, a nice basic science slide to make things easier for you.

And right now, we have about eight of these approved. And this belongs to a fabulous new class of drugs. The last class that I discussed, the iPhone XS class, right? And these are called the ICIs, or immune checkpoint inhibitors. And I want everybody in this room to have a little higher index of suspicion, and little awareness of these drugs.

Because let me walk you through this, immune checkpoint inhibitors, so this is a cancer cell, tumor cell. And we have our mechanisms in place, our immune system should fight off any foreign cells, right? So we have a T cell mechanism in place that should be able to kill off these cells.

Except the fabulous tumor cell has this life insurance policy called a checkpoint inhibitor. This checkpoint inhibitor is not for us. It's for the bad guy, the cancer cell, right? So the cancer cell has these beautiful checkpoint inhibitors. So we have certain receptors on our T cells, which help to recognize these tumor cells.

Like programmed cell death, and then this CTL for a lot of other receptors, by which it locks into the tumor cell and should kill it. Except that our fabulous tumor cell has these checkpoints on it, like the programmed cell death ligand 1, which goes and locks into our D cell receptors.

And prevents it from sucking in the tumor cell and destroying it. So guess what? We developed cells that can break its insurance policy. And these are therefore called the immune checkpoint inhibitors. They are slicing off, splicing off the tumor cells checkpoint. And so we have PD-1 ligand inhibitors, which can attach to the PD L1 on the cancer cell.

Or to the PD-1s on our T cells, and prevent this insurance policy from happening for the tumor cell. And as a result of it, the T cell can lock into the tumors and kill it. So there are a whole class of either PD-1 inhibitors or PD L1 inhibitors. And there's also another cell called the CTL-4 receptors on the tumor cells.

So depending on what it attaches to, it basically breaks off this life insurance policy off the tumor cells, and helps to kill it. And except, remember it's using our own immune mechanism to attack more, right? So our immune system ends up attacking our own bodies as well. And there's a whole slew of side effects.

And literally, you start from cerebrum to the foot maybe, and add an -itis to every organ we have in our body. And these immune checkpoint inhibitors cause ictus-- from cerebrits, to colitis, to peroditis, to adrenalitis, to you name it, they call it. Except hey, I'm here for a cardiology talk.

So let's talk about myocarditis, which was actually the least of all concern. And in pre-marketing studies, it was about 0.1% that the incidence of myocarditis was seen. I was like, don't worry about it. Hey, it's not an anthracycline.

Except, fast forward to 2016. That there were two postmortem studies came out of Vanderbilt that reported, post-mortem studies, of two patients who had undergone the same drug, similar drugs. PD L1 inhibitors. Nivolumab and ipilimumab, and they basically noticed this fabulous immune myocarditis and it killed them.

Almost like a giant cell myocarditis. Kind of folded into cardiomyopathy that killed them within days of them having getting this drug. They went into tachyarrhythmias and heart blocks, and a full following into T cell infiltration under the microscope.

Luckily, this article was 2016. Remember I saw Dr. Coleman in 2017. So I had the Monday morning quarterbacking to help me. And I said, oh god, he's gone into complete heart block. New cardiomyopathy. No coronary disease, no PE. This as Keytruda induced immune mediated myocarditis.

And so I had any GM article to back me up where the patients died. Because they were given one milligrams per kg of methylprednisone. I'm like, I'm going to bombard them with something bigger. And so I bombarded him with 2 mg per kg of methylprednisone.

Same admission, repeated an echo, a week later his EF improved. Unfortunately, heart block was irreversible, so we ended up giving him a pacemaker. He was discharged to hospice, and he need of died seven months subsequent later.

Got a beautiful letter from his wife. He died in hospice in good spirits. And so we became part of a registry. This was the first article coming out of this registry where we've pulled together with MSKCC and Brigham. And we've put together this data where we've started seeing these immune checkpoint areas, which such a [INAUDIBLE] for these end stage oncological patients.

And we've seen in our registry data so far, and trust me this number is rising, that myocarditis is more, immune mediated myocarditis is more common than we thought initially. And here's the caveat.

And this is why mechanisms are so important to understand. Guess what? On our registry data we saw that most of his cardiomyopathy, at least patients can get these drugs for years, right? So most of this in immune immediate myocarditis was occurring the first three months.

Echo doesn't pick it up. Your LVF might decline much later. MRI doesn't pick it up, Unless you do the MRI after five days. Guess what is a best screening tool for ICI-induced myocarditis? Good old EKG and troponin.

Good old EKG and troponin was positive in plus 90% of these cases. So all we need to do is when they come in first three months with ICIs, asymptoms of course. But get an EKG and get a troponin in them then, after every dose that you give them. And you might be able to pick up subclinical myocarditis.

Whether or not we can re-challenge them, we don't know. But based on our registry data, this is what we suggest that if they have an elevated troponin, abnormal EKG in the first three months after ICIs. Please consult cardio oncology. Then there are drugs like carfilzomib that you might have heard of, which is used widely in multiple myelomas.

Is a game changer in myeloma patients, right? And we started noticing a huge amount of heart failure, ischemia, hypertension, dyspnea. These are these are like initial trials, which weren't even designed to pick up cardiotoxicity.

And we noticed this in the ASPIRE, et cetera trials. And so I had this fellow rotating with me, he had his old basic science lab in Detroit. And I told him, like we have to understand the mechanisms of the drug. Take it to your lab, feed it to the rats, and see what happens, right?

So he took it in the rabbit models. And basically, we saw this intense amount of acetylcholine endothelial depend vasospasms. Similar to TKIs, but intense amount of vasoconstriction, which we feel is a mechanism of action off carfilzomib, where it causes heart failure, hypertension, chest pain, shortness of breath.

Just because of the increased coronary resistance, vascular tone, and vascular reactivity that we saw in these studies. And we were actually ended up being cited in a lot of subsequent carfilzomib cardiotoxicity data. And therefore, when people come to be the carfilzomib toxicity, I bombard them with some dialators and sympatholytics, understanding the mechanism of this.

So remember, this is just a little blurb of how different cardiotoxicities happen. I do want to put in like two slides about all of you, who are rotating through ICU. And you want to see something called cytocrine release syndrome, or CRS. And you want to hear this word, CAR-T therapy, right?

Again, immunotherapy has blown the oncological world. And it's also blown my world, because I end up dealing with the cardiac effects of this. So let me, again, walk you through our very busy slide. So CAR-T therapy is used in a lot of advanced lymphoma, leukemias, and myelomas, right?

These people have failed all kinds of chemo, it's lifesaving for them. End stage life saving. So we take the patient's own T cells, right? We take them up, take them to a lab, and we genetically modify that by introducing an inactive virus into the patient's own T cell, making the patient's T cells express something called CARs, which are basically chimeric antigen receptors.

And now our T Cell becomes a CAR-T cell. And these are beautiful CAR-T cells because these CARs on the surface of the T cell when multiplied, and reintroduced back into the body of the patient with the leukemia, lymphoma, myeloma, now specifically targets the cancer cells and kills them off.

Because these CARs are specifically designed to be antigenic, or antibody to the antigenic cancer cells, right? Beautiful system, beautiful mechanism. Lifesaving, except we are introducing these super activated, ready to go CAR-T cells in our body, which will activate our cells and our immunotherapy as well.

And it's basically notorious for an IL 6 mediated cytokine release syndrome. It's basically like the cousin of a horrible septic shock. Vasodilatory shock. And as a result of it, myocardial depression, and cardiomyopathy similar to stress cardiomyopathy can occur.

And the treatment here is, besides pressers et cetera, is you bombard them with an IL 6 blocker, since it's IL 6 mediated. You bombard them with tocilizumab. We do have formulary in Sinai, and steroids. And then of course, standard heart failure therapy when their blood pressure is stable.

But the caveat here being you'll see a lot of them come to me for clearances before, and you do not make the mistake of doing this. I know you won't. But because of the CRS, these people are knowing CAR-T, the potential of having CRS. Their blood-brain barrier and vascular breadths of very friable.

So they cannot be on anti-coagulations, or god forbid, they want AFib, or whatever else. You can't anticoagulate them. And you can't give them dual antiplatelet therapy. And we discontinue that for about 7 to 10 days, before CAR-T therapy. So just to put your radar out, it's like what's CAR-T why am I just continuing the eloquent, just for you to know that.

And also remember, Takotsubo's, which I'm sure everybody around this room is very familiar with, the broken heart syndrome. Doesn't just happen at traffic stops, and heartbroken women. It happens a lot in our oncological patients. It's a very stressful situation.

So this is a typical, apical ballooning syndrome named after the Japanese octopus pod. I don't know how many of them still use it. But that LV gram and the echo still looks where the rest of the heart's OK. But the apical segments of the left ventricle, the balloon out like an octopus pod.

And the incidence of Takotsubo's in our cancer patients is very high. In fact, they actually did a five-year nationwide study in cancer patients, and they noticed that about one third of cancer patients can have Takotsubo's in cardiomyopathy. So when you don't find anything, oh they're on CAD.

They don't have PE. They're not getting cardiotoxic chemotherapy. There's always a possibility of Takotsubo's in these patients. So I hope I've confused everybody around this room. And so we're talking about good stuff now.

Hear the horror stories are over, every drug is horrible. Every drug's mechanism is different. I don't understand this basic science stuff. Let's try to prevent it, right? And that's where you guys come in. And really, the prevention is key.

And you guys are key. Because they're got to come to me only if you guys send them to me and my colleagues, right? So understanding cardiotoxicity, and keeping a window of suspicion very, very broad is very important. And really, whether it's anthracyclines, the risk factors are pretty much the same.

It's very similar, where we made a little bit broader than framing it. But really, it's all common sense stuff. Hypertension, radiation, coronary disease, age greater than 65. Whether it's HER2 therapy, or VEGF inhibition, or anthracyclines, the point I want to drive home is please don't not treat their dyslipidemia, their hypertension, their CAD.

Just because somebody has cancer doesn't mean you give them a death warrant from your side for treatment. OK? Everything goes hand in hand. This is not the time to say oh, poor thing, let them go through chemotherapy, everything's going to interact with things.

I don't want to start them on a statin. I don't want to start them on beta blocker. This is a time when you start them. You treat their heart failure. Treat their latency AD. Treat the dislipidemia, because A, only all these concomitant things add to their cardiotoxicity.

Secondly, they can beat the cancer. Remember, most of them to beat their cancer, and they're going to live longer. And then you would have to deal with the late cardiotoxicity, in the late cardiovascular effects of these patients. Right?

So please treat them. And what tools do we have to detect it early, right? So patient education is key. And really, a lot of my time was in counseling these patients, going through the scenarios of what the incidents, and possibilities of developing cardiotoxicity.

And patient education is key. Let them know, hey, be aware of your symptoms. You know what? We don't do a good job of identifying symptoms. Maybe we don't have the time. We don't have the patience. But really, if you leave it to the patients, and believe it or not, nurse practitioners.

They're excellent. If you leave it to our little helpers, and our patients, they will do a much better job of reporting symptoms, and picking up early cardiotoxicity than we do off of it. And biomarkers, we love sitting around the computer, and we'd rather sit on our computers, and analyze data than talk to our patients.

So yes, biomarkers help. What about BNP? Can BNP protect future heart failure? And the data is kind of equivocal. We do know the higher the BNP level, it probably have worse outcomes later on. We're not-- we know they have higher MACE.

But we're not sure if it predicts decline in LVF. Troponin, however, is a little bit more robust predictor, right? And elevated troponins are probably predicting cardio toxicity earlier before the LVEF declines.

Echo. Yay, echo of course huge amount of data with echo. And remember, the definition CTRCD. 10%, 55%, right? Problem with LVF, if it's already too late. If you're going to hang your hat on the LVEF of declining for cardiotoxicity, the ship's already sailed.

And not just that. We are very bad at giving an exact number of LVEF to our colleagues, or oncological colleagues. Trust me, like half my emails and calls go in saying the EF was 75% like a month ago. Now it's 65%. What do I do?

It's a 10% decline. And you know, I take responsibility for this, in the sense that all our colleagues, and this is lead really a meta analysis of patients ongoing cancer chemotherapy. How there's, no matter how I calculate the EF, and these are different methods, biplate symptoms.

With contrast, without contrast. Triplate symptoms, no matter how I calculate the LVF, is a huge amount of inter and intraobserver variability in predicting LVEF. And I could go into the room blindly, 45 minutes, I might read plus minus 2% and 5 percentage points of those same patients' EF, right?

So the only method of LVEF reading that has a least interim [INAUDIBLE] variability, 3D LVEF? How many of our echo reports hav 3D LVEF? 0, probably just a few research studies. So really, there's a lot of intra and interobserver variability, and already the ship has sailed.

So the two things which are able to predict cardiotoxicity, or LVEF decline are A, troponin. If troponins are positive, they might predict that three months later, the LVEF is going to decline. And there's something called strain.

And you might see this in our echo report. Strain might predict a decline in future LVEF. So what is strain? Oh my god, another horrible word, right? So let's just say that straight is a good word.

Strain basically means deformation. And the heart really insistently deforms. It's a good thing. And the healthier the heart, the more vigorously it's going to deform in four axes. In a longitudinal axis, in a circumferential axis, and a radial axis, and in a transfers axis.

So it's like a switch, switch going on in four different vectors. And that deformation, or shortening during systole is a good thing. The more vigorous and healthy your heart, the better the strain is going to be.

So let's just stick to the longitudinal strain, because it's been validated in cancer chemotherapy patients. So say this is your sarcomere in diastole. It's 8 centimeters long from base to apex. And it deforms, good word, into systole in 6 centimeters. So there's a 2 over 8, 25% deformation in the longitudinal axis.

This is a good, vigorous heart. So if this was affected by chemotherapy, this deformation or shortening in the longitudinal axis, i.e. longitudinal strain, this will become less and less. So if I put it in a bullseye map with different segments of the heart model, and put it in an averaged number called GLS.

So you are going to see this in our echo reports called global longitudinal strain, where all segments of the heart are represented. So any number above minus 18, if it deforms by more than minus 18%, it's a good thing. It's a good, vigorous heart.

So all these numbers, minus 28 minus 31, 32 great. Minus 8? Not good. See how it can pick up segmented variations as well. And we've seen in a meta analysis of 33 patients that this is able to predict a decline in LVEF, even before the LVEF declines.

And a GLS might be one of the earliest markers of cardiotoxicity that we can get from echos. And for example, there's a patient who started off with tocilizumab therapy, normal GLS of minus 25, averaged out. And then got trastuzumab therapy three months later, and the GLS had declined to minus 14.

And if your GLS declined by more than 15% over the patient's baseline, that means an abnormal to a point of less than minus 18 that is an abnormal GLS. And that might predict future decline in LVEF.

So look at it as a crystal ball for future cardiotoxicity. Right? And so the ASE, taking it beyond its crazy definition of CTRCD, now besides CTRCD, has put it in that if your GLS declines or baseline by more than 15%, that might indicate subclinical LV dysfunction.

OK, great. What do we do with this stuff? What do I do, tell them to stop chemotherapy? So well, we're working on it. But there might be data emerging such as the upcoming SUCCOUR trial which is suggesting that maybe, guided by abnormal GLS's or declines a GLS, if we initiate cardio protective therapy, ACE inhibitors and beta blockers, we might interrupt or prevent future cardiotoxicity and be able to, without fear, give these patients cardiotoxic chemotherapy.

So yes, everybody gets a bill, right? So what pills should we pop? Huge slew of data, all small trials. Caveat, I'm putting it in a busy slide. Not going through all of the stuff. Smaller trials, 30 patients, 40 patients, 80 patients at best. Off primary preventive, primary prevention.

LVEF hasn't declined. We're giving them cardiotoxic chemotherapy, losing anthracyclines and trastuzumab. And there's data for ACE inhibitors, ARBs, beta blockers, the Overcome trial was studied in bone marrow transplant patients where we bombarded people, all comers, without hypertension, without heart failure, Coreg and enalapril.

And those who got Coreg and enalapril versus who don't had less declining in LVEF after BMTs. The Prada trial came up two years ago, which showed candesartan was primary prevention in breast cancer patients receiving anthracycline tocilizumab. Metoprolol did nada, nothing.

CECCY trial with Carvedilol did not reduce events. But there was a reduction in troponin levels and diastolic dysfunction. Bisprolol has shown to be consistently preventative. Nibivolol emerged in the MANTICORE trial as well.

And so basically, let me size the whole thing into one slide, that first of all, please risk assess them and see whether we can treat, and we should treat the cardiac risk factors. Decide on the drug and the dose. Try changing the infusion regimen.

Use, try to think about particular predictive therapies like dexraroxane and acryline inhibitors and cytoxin. Maybe you want to switch dosage forms, and I'll go with doxil in two seconds. ACE inhibitors and beta blockers.

So there's a lot of ways of preventing cardiotoxicity, right? And I wanted to touch a little bit on the doxil old story. Doxil, and you must've heard of it in sarcoma patients, is basically doxorubicin. But it's encapsulated in liposomes. So it becomes a big molecule.

It's the same doxorubicin, so is able to go in and kill your cancer cells. But it's a very big molecule, so it's not able to penetrate into the preformed vascular beds of the heart, which are narrower, versus the vascular beds of cancer cells are huge.

So they enter into the cancer cells, but they're not able to enter into the myocardium just as well. And so the cardiotoxicity is better. So alternatives are there. There's preventative role of statins that we're studying now. So don't be afraid of putting them on a statin, unless there's like huge, strong interaction.

Flu vaccine, don't forget. And this came out of our registry data from the ICIs, that patients who received a flu vaccine within six months of them having received one of the checkpoint inhibitors had less myocarditis, has had less immune-mediated myocarditis.

Again, we don't know the exact mechanism. Whole immunotherapy stuff. But give them their flu shot. Give them the ACE inhibitors, their beta blockers, their statins. And don't forget of a cardiotoxicity. Since we're short on time, I'm just going to give you a little teaser of all the slides.

I'm going to open up a Pandora's box. Give you a whole slew of drugs that causes ischemia, with just one caveat. Remember, just because patients with cancer have low platelet counts, and they bleed, does not mean that it can't get ACS, OK?

Is thrombocytopenia, it's not a protectant. You do different things to protect them in ACS. We might use a radial approach. We might use bare metal stands. There are new strands coming, and aspirin is OK to use as long as that platelet counts are OK, more than 10,000.

I know it scares a lot of people are this room, but yes, I've used aspirin with platelet counts 20,000. Clopidogrel, a little bit higher platelet counts are needed. And the other antiplatelet agents you want to have platelet counts higher than 15,000.

And newer drugs such as polymer free stents are coming up, where we might need just one month of dual anti-plately therapy, and get away with it. And remember, so just give a synopsis, if you're just using aspirin for primary prevention and the patients of thrombocytopenia before undergoing drugs and [INAUDIBLE], please stop the aspirin, OK?

Bare metal stent, it's OK to go to aspirin for platelet count for 20,000 for sure, in some cases more than 10,000. If you have a drug eluding stent, please try to delay thrombocytopenia, bone marrow transplant, et cetera for 30k at least, for six months.

So that the platelet counts don't go above 30k. If you're using anti-coagulation, please stop or half the dose of lovenox, so low molecular weight heparin at 20,000. And you have the dose adjusted. And of course, I'm always there, available to ask to answer questions about dose adjustments, et cetera.

But remember that not only is cancer causing clotting, a lot of the chemo causes thromboembolism as well. And these are latest slides that came out in the last six months. So everybody knows from the clot NAGM trial, right, that low molecular weight heparins to superior to Coumadin.

So Coumadin for constipation is out, right? Drug interactions makes them clot again, we know that. And we saw in the sub-studies for edoxaban, rivaroxiban, and dabigatran that no acts are actually probably superior to Coumadin, in thromboembolism, right?

But we weren't sure if the NOACs hedged against low molecular weight heparins are equal, better, worse, or not. There was a chest meta analysis in 2015 that suggested that maybe no access superior to lovenox. And low molecular weight heparins.

And so fast forward to 2018, last year. We had two trials, in*NEJM.* One was a select D trial in the [INAUDIBLE]. You guys might want to read up on that, one starting adoxevan versus dalteparin. And the other one, rivaroxiban versus dalteparin. And guess what?

Yes, less recurrent VTE with NOACs, but much more bleeding. And much more bleeding which patients? GI and GU cancers. So here is what I do as a rule of thumb, is that I love NOACs, much more easier to use than low molecular weight heparins.

And of course, the less VTE. But if they have GI and GU tumors, I stick to low molecular heparins. But if they don't have a GI, GU tumors and I'm using it, then it's probably best-- it's OK to go with low molecular-- with NOACs. And we recently, just four weeks ago, two trials came out in *NEJM,* the Avert and the Cassini trials.

And this is primary preventions, not VTE treatment, it's prophylaxis in walking, talking patients, in cancer patients, not in patients. And basically, avert was apixaban to prevent VTE.

Half dose, not 5 IBD, 2.5 BID, which lowered the risk off prevention of VTE over 180 days. And rivaroxiban was also 180 days, half dose again. 10 milligrams once a day. Did not statistically lower VTE incidence or death due to VTE.

But there was a reduction, a trend towards reduction in VTE. And the risk of major bleeding in both studies was twice, so 2% versus 1%. Not horribly high, but high. But remember, we're using prophylactic doses here. Huge amount of drugs causing bradycardia.

Please don't put in pacemakers into those patients. Just go through the list of drugs that cause bradycardia. Arsenic is a big one for QT prolongation. But there's a whole list of QT prolonging drugs. Atrial fibrillation causing drugs.

And remember, it's a tough group to manage. Not only can you not apply CHADVASC course to them. They bleed more, they clot more. We have to think outside the box. And I want to show you a horrible drug called ibrutinib, which like Jekyll and Hyde.

Fabulous drug, use it a lot of lymphatic malignancies. But if somebody with a ibrutinib goes in, if please call me or call one of my colleagues, because they have a huge incident, about 20% incidence of atrial fibrillation.

And you cannot give them half the drugs. You can't give them amiodrone. You can't give them deltis. You can't give them anti-coagulation with Coumadin. There's a whole lot of drug interaction, bleeding, clotting, et cetera. And it's a very difficult situation to treat when somebody with ibrutinib goes into AF.

A whole lot of drugs causing pericardial effusion, and two seconds on radiation induced heart disease, which less amount of my patients that I see. But don't forget that if you've been exposed to left chest radiation, whether it is mantle radiation, or breast radiation, if patients have exceeded 30 gray units cumulative, they are going to develop, high chance of developing radiation induced heart disease.

Again, board question. Very rare to happen immediately. Most of the effects, the two big ones, CAD and radiation-induced valve disease happens after 10 years. So CAD happens after 10 years, and radiation induced heart disease usually happens after 20 years.

And so that's the way the screening should start. So we tell people to come in for an echo between five to 10 years of their high risk. And after 10 years, if they are low risk for echo, and for screening for CAD and radiation induced heart disease. So let's not relax when all the bad stuff is over, and now let's see my patients poor bad stuff.

And this a patient with routine, I very few oncological emergencies. But when somebody has-- this patient had an abnormal echo, sent for a TE. And then they call me panicking, there's this whole huge, it's a TE study. This is the right atrium tricuspid valve, right ventricle. The shiny structure here is a port. Patient had metastatic HER2 breast cancer, undergoing trastuzumab.

Huge floating around structure here. We don't know whether it's thrombus, or a cancer, right? And so we actually took the patient to the OR, because it is huge embolic potential, we can wait for anticoagulation to act. Luckily, it turned out to be a thrombus, and the patient had a sternotomy.

But luckily, we had two. It was a huge thrombogenic potential. This was a sadder story. Patient with angiosarcoma of the liver, with a huge pericardial effusion. You can see this echo free space here. But what's more scary than the large pericardial effusion is this is the right ventricle. This is the left ventricle.

There's this amount of gunk sitting here in the right ventricle. And this kind of cavitation almost, and we're kind of worrying, is this cancer inside the right ventricle? Or has the cancer gone through the RV free wall and is now causing this big cardio effusion? Luckily, we give contrast to this patient, and the contrast, which is here, does not extravisate into the pericardial space.

Luckily, this was a separate pericardial effusion, and not a rupture of the RV free wall. So just sign up size, everybody hopefully in this room can distinguish between type 1 and type 2 cardiotoxicity, and the rest you leave to me. Should know early detection prevention, monitoring, treatment is key. So those protocols should be established, and be aware of these.

Especially the non-CHF cardiotoxicities. Don't forget your radiation patients. And we do understand a lot of the cardiotoxicities, we just don't know what the prevention and treatment can be uniformly applied, because it's not a uniformed mechanism of action. And maybe, some trials like the SUCCOUR trial will let us understand if tools such as GLS less can be used to intervene earlier.

And what is the cost of it all? And are we allowed to say no to patients getting this chemotherapy, right? Just too many m not enough in the guidelines. That we have a lot in, by the way, the ACCHA are lacking in that. And again, the cost factor is huge, right?

So I told you about that the slide with HER2 positive trastuzumab therapies. So everybody gets an echo baseline, and every three months when you're on trastuzumab. That's five echoes per year, right? For a patient with HER2 positive breast cancer. I'll just show you the math with one of them. So Medicare reimburses us $570 for an echo. And they're about, in 2017, there were about 250,000 cases of breast cancer, out of which 63,000 were HER2 positive.

So I'm giving them trastuzumab, right? And so that means per patient, just the echo part is costing us through $3,500. And does every patient need like five echos, four echos a year? What are the echos say in the beginning, and like somewhere in the middle were fine? If you take away one echo for these patients, we can save about $36 million per year on just these breast cancer patients.

So it's not an easy-- it's easy said and done, based on these smaller trials. Or let's intervene, let's get GLS. Let's put them on ACE inhibitor and beta blockers. Let's follow them an echo in four weeks. But really, the cost-benefit analysis, I know every patient's important, and that's why pharma genomics, and really personalized medicine, and going by who is susceptible, who needs more monitoring, who needs more intervention is where we're heading towards.

And really, people in this room basically, who should be referred to cardio oncology, you know that people with higher risk factors. You should be slightly aware of the cardiotoxicities while they are undergoing treatment, and don't forget the late cardiotoxicity patients who have been exposed to anthracyclines, radiation et cetera.

And so how are we doing in cardio oncology? Here, huge amount of patients. We saw close to 3,000 patients last year. We've initiated a lot of monitoring protocols, GLS protocol going to see in our echo reports routinely, and patients getting chemotherapy. A lot of research activities going on.

And if anybody wants to go to resources, we have a couple of chapters and a lot of books. And from that roller coaster ride in the beginning slide, hopefully this roadmap helps you clear a little bit of the cobwebs I introduced. Thank you, and open for questions.

[APPLAUSE]

SPEAKER: We had a little bit of a late start. So I'll invite everyone up for questions, and let's thank Dr. Sahni.

[APPLAUSE]