



Deciphering the Cardio-Toxic Effects of Cancer Treatment

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Welcome to Yale Cancer Answers with doctors Howard Hochster, Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers is our way of providing you with the most up-to-date information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week Dr. Hochster is joined by Dr. Lauren Baldassarre for a conversation about cardio-oncology. Dr. Baldassarre is an Assistant Professor of Medicine and Cardiology at Yale School of Medicine and Dr. Hochster is a Professor of Medicine and Medical Oncology, Associate Director for Clinical Services at Yale Cancer Center and an expert in gastrointestinal cancers.

Hochster Dr. Baldassarre, can you tell us a little bit about your background and how you came into this kind of unusual niche of medicine at the intersection of cancer and heart? As a medical oncologist, I give people chemotherapy and I think that hearts are just to pump chemo around the body, you have a different perspective I think?

Baldassarre Yes. While I am a cardiologist by training, during my training, I focused a lot on advanced cardiac imaging and also had an interest and some experience in prevention and women's cardiovascular disease, and so I think that this field sort of naturally ended up putting all those things together for me because a lot of what this field focuses on, at least initially with the development of the field of cardio-oncology, was the concern for some of the cardiac side effects of some of the treatments that are given for breast cancer, and of course now that field has expanded to involve patients with many other cancers and many other therapies that are given, but initially for me, this was a way to bring together my interest for prevention, because I really think that a lot of our focus in this field should be on prevention of these patients developing cardiac side effects, and we do that via monitoring them and medical therapy and sort of supporting them through to get the best treatment for their cancer, and there is also a large role of advanced cardiac imaging with advanced echo, also cardiac MRI, cardiac CT and some nuclear imaging as well. And so, this sort of naturally became an interest for me as the field was becoming more popular towards the end of my training, and I had some opportunities to do some additional training at a cancer center and with some advanced cardiac imaging in this field.

Hochster I was going to ask you what you meant by advanced cardiac imaging, but I think you kind of covered that a bit. So, that is really using mostly, cardiologists use EKGs and they listen to the heart and they get ultrasounds, but you are talking about using tests beyond even an ultrasound, using CAT scans and MRIs to look at heart function.

Baldassarre Yes. The sort of mainstay of the way that we evaluate at baseline and monitoring and after treatment with these patients is with ultrasound, with echocardiography, but

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echocardiography has had a lot of advances over the last few years. We now have something called 3D echocardiogram and also some additional techniques that we can use with ultrasound; for example, something called strain imaging that starts to look a little bit closer at the cardiac function in a bit more detail and the goal of that is to ideally help us to identify when someone, a patient, is at risk for developing some cardiac dysfunction, but to detect these early signals before that dysfunction actually occurs, so we can take that opportunity to try to prevent that from happening, and that can be done with advanced echocardiography as I just explained, but also cardiac MRI to look at function and also a little bit closer at the tissue of the heart muscle, also with cardiac CT if there is a question of needing to evaluate some of the coronary arteries if there is a question of ischemic heart disease and then nuclear imaging – we use most often for stress testing when indicated.

Hochster Is cardio-oncology a new field? How many people focus on this? You do not find that in most community hospitals, for example.

Baldassarre Correct. The field, or at least the interest in patients who were receiving potentially cardiotoxic therapy, started back in the late 70s, early 80s and actually some of those initial studies were done here at Yale in the nuclear cardiology department, where they first started to identify that there were significant risks, cardiac effects, from very high doses, many of these high doses we do not use routinely anymore, and that was first identified, but over the last 5 or so years, I would say 5-7 years, it has really come to light with more research that has been done and published, that has shown us that there are cardiac side effects with some of the breast cancer therapy, but also some of the other therapies that are being used. And it has become even more important than it was decades ago, because the survival of these cancer patients, specifically breast cancer but other cancer patients as well, has significantly improved as the treatment for these cancers has improved, which is great. And so, what we are seeing now is that the concern for cardiac side effects is not just an immediate concern but the effects of these drugs can be seen years out and actually some data has shown that patients who have received some of these therapies, they are living many, many years and being cured from their cancer but years out, there are increased risks for cardiovascular side effects compared to patients without that therapy. And so, now we are wanting to focus more on their cardiovascular health because they are living longer and that is a good thing.

Hochster I think going back as you said from the early studies, it helped us describe some of the effects of a drug called doxorubicin or Adriamycin, and you said high doses, but really in that case it was high cumulative dose, right? So, people who got a lot of treatment for many months and who were responding to the treatment and continued to get it, it was a problem as it had started to affect their heart, and do we still have problems today, how do we usually handle that?

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Baldassarre We are not seeing it in the same way that it was administered previously, but we are still seeing effects in patients and actually some of them even at lower doses and earlier on in their treatment. So, it is still a problem. The exact number is difficult to pinpoint because when you look back at some of the major studies, the way that they reported cardiac side effects was different throughout. So, the risk is real but it is low, and I think the most important thing is to identify who are the patients at risks and get them the proper sort of risk assessment at the beginning, be able to have informed consent conversations with the patient, the oncologist, the cardiologist about what are the risks of the therapy and what are the risks of the breast cancer? It is actually pretty rare that we would ever recommend somebody to not get the right therapy or the best therapy for their breast cancer. We usually try to just support them as much as we can and whether that be with medical therapy or a different type of monitoring or more frequent monitoring, but every once in a while, patients who have severe cardiac problems develop a severe problem with their therapy, and we may need to stop for a minute and reassess moving forward.

Hochster So, before you get into some of the drugs that cause the problems today, what are the risk factors of this? What should patients know about their heart when they start any kind of cancer therapy today, or who should be more concerned about their risks for cardiac problems versus everybody else?

Baldassarre These patients, just like all patients, should know their cardiovascular risk profile, which would include knowing their family history, other diagnoses they may have or need to be evaluated for – for example, diabetes, high blood pressure, high cholesterol, all of that screening should happen. In general, I think any person who is going into therapy that may have any cardiotoxic side effects regardless of their risk factors should consider being evaluated, if not a cardiologist, at least by having a discussion with their oncologist. But for sure, patients who already have a pre-existing cardiac condition, for example, coronary artery disease, history of heart attack, myocardial infarction, valvular disease, they are higher risk, and patients with one or more cardiovascular risk factor like diabetes or hypertension, they are higher risk than a patient without and those patients really should have an evaluation, if not a thorough evaluation with their oncologist, then perhaps also evaluation by a cardiologist.

Hochster So anybody who has known coronary artery disease, for example, that would be the most common thing probably, even if they did not have an MI, what kind of pretreatment evaluation do you think somebody like that should be getting?

Baldassarre Every patient is different depending upon clinically what is going on with that patient at this time, and what is planned for them as far as chemotherapy, perhaps they need surgery. Sometimes, it will be appropriate to do an assessment of the status of their coronary artery disease, sometimes with functional stress testing whether that be nuclear echo, MRI or

taking a look directly at the coronary arteries via procedure, via coronary CT angiogram, and like I said, it depends on the status of that patient; how are they doing, what symptoms are they having and how high risk is the therapy going in.

Hochster If you see one of these patients before they start chemotherapy, what is the role of the cardiologist then and how do you interact with their oncologist?

Baldassarre We first do a full cardiovascular risk assessment, and we discuss checking their blood pressure, heart rate, seeing their lipid profile, reviewing all their medications, seeing what type of recent testing they have had done and for some patients it may be appropriate to start them on a new medication, medications for their blood pressure and/or heart rate and that can be cardioprotective, things like beta-blockers or ACE inhibitors when appropriate.

Hochster Do you have to usually do imaging tests before, EKG, echos?

Baldassarre We do an EKG, we do echos at baseline. Depending upon the echo, if it is completely normal, good quality echo, often that is enough at the baseline. If there is any abnormality on the echo, for example, any decrease in any of the cardiac function, then we usually go next to a cardiac MRI to fully assess the function again and to look a little bit closer at the heart muscle to see if there is any evidence of any prior scar or something like that.

Hochster Thank you, Dr. Baldassarre. We are going to take a short break for a medical minute. Please stay tuned to learn more information about cardio-oncology with Dr. Lauren Baldassarre.

Medical Minute

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The American Cancer Society estimates that more than 60,000 Americans will be diagnosed with head and neck cancers this year. Although the percentage of oral and head and neck cancer patients in the United States is only about 5% of all diagnosed cancers, there are challenging side effects associated with these types of cancer and their treatment. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center to test innovative new treatments for head and neck cancers. In many cases, less radical surgeries can preserve nerves, arteries and muscles in the neck enabling patients to move, speak, breathe and eat normally after surgery. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital. More information is available at YaleCancerCenter.org. You are listening to WNPR, Connecticut's public media source for news and ideas.

Hochster Welcome back to Yale Cancer Answers. This is Dr. Howard Hochster, and I am joined tonight by my guest, Dr. Lauren Baldassarre, and we are discussing cardio-oncology. Dr. Baldassarre,

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you were previously discussing breast cancer and some of the drugs that caused cardiac problems, so I guess the original drug for this is doxorubicin or Adriamycin, they still use that in breast cancer, especially for adjuvant therapy, right? What are the cardiac issues with that drug and what do patients need to know about that?

Baldassarre The main concern as far as cardiac side effect from the anthracyclines is that there is a potential to cause cardiomyopathy or decreased heart function, and that is something that we monitor by getting a baseline ultrasound of the patient's heart and echocardiogram at the beginning of their therapy and then we monitor with serial echocardiograms during their therapy and after, and that is to look at the function of the heart. Most patients do well and there is no problem with tolerating the therapy, but there is a small percentage of patients that can develop a cardiomyopathy or decrease in the function of their left ventricle, which is the main pumping chamber of the heart, and for those patients, depending upon how much the function has decreased; if it is mild, often we are able to get some cardioprotective medications on board and continue with the therapy, and in less common circumstances, the cardiomyopathy or decreased function could be more significant, and in those cases we often hold the therapy at least temporarily, get these medications on board, then we re-image with an echo or potentially cardiac MRI, and if there is recovery of some of the function, we are able to continue, and in rare cases, if the dysfunction is very severe, those will be cases where we actually may not be able to continue with the therapy.

Hochster So, every woman who is getting this kind of AC adjuvant therapy, even in the 4 doses that are normally prescribed with AC, they should get a baseline echocardiogram? Even if they have no cardiac history?

Baldassarre Yes, even if they have no cardiac history.

Hochster And a follow-up?

Baldassarre Yes and a follow-up after therapy is completed, but also, they should be serially followed after that. For our breast cancer patients that we see here, we monitor them closely during and after therapy and we will see them again about 6 months after and then at the 1-year mark. If they have no cardiac complications and there are no concerns, we ask them all to come back yearly for monitoring. If there were any cardiac complications or concerns, then of course we would follow those patients more closely.

Hochster I want to emphasize, while most patients who get that drug for many, many months, more than 6 months, will eventually get some cardiac effects with the doses that we prescribe today, the incidence is really low – like 1%.

- Baldassarre It is hard, as I described earlier, to put an exact number on it because the way that the cardiac complications are reported and the different trials, there is some variation. We give usually an estimate of less than 5%.
- Hochster Less than 5%, so very low. Then, radiation is used a lot in the adjuvant therapy of breast cancer. When we say adjuvant therapy, we mean the other treatments we give after surgery. So, what about radiation for people who have left-sided breast cancer, is that a problem for the heart?
- Baldassarre It can be, there can be a concern for increasing the risk of cardiomyopathy, the decreased function which we just talked about. The other two concerns with radiation, actually a few other concerns; one is that there could be effect on the valves of the heart and from radiation therapy, the valves can become a little bit thickened or fibrotic, and overtime, that could potentially lead to some valvular disease – either with causing some stenosis or tightness of the valve and also potentially causing some regurgitation or a leakiness of the valve. There also could be effects onto the lining of the heart, which is called the pericardium and that lining, similar to the valves, has a potential to become inflamed with the therapy and then overtime some scarring or fibrosis, which could be an issue. The other concern is potential effects on the coronary arteries themselves leading to some coronary artery disease.
- Hochster I just want to emphasize, today the way radiation is done for adjuvant therapy of breast cancer, they have better ways of delivering the radiation in that most of the time they can come in at an angle that includes very little of the heart, maybe just a corner of the heart at most, so it is not as much radiation to the heart itself as they used to give with breast radiation.
- Baldassarre Correct, and so those patients, even though it is important to know that there could be an increased risk to offer them some evaluation, there are not recommended guidelines for serial monitoring as much as there are with the other therapies that we talked about because the risk is relatively low.
- Hochester And then, about a third of women with breast cancer today, we find that they have an elevation in the protein called HER-2 and there is an antibody for that, trastuzumab or Herceptin, that also has some unexpected effect to the heart. Can you tell us about that a little bit?
- Baldassarre The concern for that is similar to the concern with the anthracyclines as far as wanting to monitor any effects on the function of the heart muscle and the cardiac function, a similar risk profile. Initially, it was thought that this type of cardiotoxicity or potential decrease in

the function of the heart with the Herceptin or trastuzumab was more of a reversible type of effect and that with the anthracycline base, it was not reversible. There is actually more data coming up that that is not true, that we do not really know which one is and is not reversible, but we do know that the combination of the two given together can increase the risk of developing a cardiac complication like cardiomyopathy.

Hochester So, if they get the doxorubicin and Herceptin, that could be more problematic potentially?

Baldassaree Correct, yes. But there is so much that we are still learning about this and trying to figure out and then discover, and I can tell you that I have had many patients who have developed decreased heart function, cardiomyopathy, on one of the agents or after receiving both, and many of them actually have recovered their function after therapy. So, I think we do not know what is reversible and what is not reversible, but what we do know is that we can monitor them more closely, get medications on board to hopefully protect their heart and we are seeing good outcomes with those patients who are being closely followed.

Hochester It is a little unusual for antibodies, we have antibodies against EGFR which is called HER-1, it is a little bit in the same family, but that does not cause any problems with the heart, do we know what it is about the Herceptin or trastuzumab that specifically effects cardiac function or cardiac muscles?

Baldassarre We do not know for sure, there are different thoughts out there about what it may or may not be. In general, at least when I explain to patients, we think about it like the therapy that you are giving at that time and one theory is that it is effecting the heart cells ability to accommodate stress and so it may be sort of a multiple hit type of scenario where it is removing the cells ability to accommodate stress and then you are adding an agent that is causing stress, or for example high blood pressure could be that additional stressor that the cell is not able to accommodate for at that time. That is one of the reasons why we are very aggressive here about controlling blood pressure during the time of therapy. Often, we think of hypertension, high blood pressure as a long-term problem in patients, and so sometimes they think it is not important right now to worry about my blood pressure, I am going to focus on my breast cancer, and actually, we think it is incredibly important to control it at that time to decrease the amount of stress that the heart has seen.

Hochester Even if somebody gets the AC with doxorubicin and they get the trastuzumab in the adjuvant setting, this kind of postoperative preventative treatment, the incidence of developing one of these cardiac complications is still pretty low?

Baldassarre It is. I would give you the same range, I would say less than 5%.

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Hochester And I just want to add for listeners out there that trastuzumab or those kind of anti-HER-2 antibodies are also proven for stomach cancer, gastric cancer, and they are occasionally used for other tumors that overexpress HER-2, so if you are getting trastuzumab for any cancer, not just breast cancer, this is a potential cardiac issue. We are also now seeing biologic-type drugs, inhibitors of signal transduction, that seem to be affecting the cardiac conduction pathway. Can you tell us anything about what people need to be concerned about with some of those drugs and what the concern is?

Baldassarre The concern is essentially what you just mentioned as far as causing some conduction abnormality or a prolongation of the QT, which is one of the parameters that we look at on an EKG. Usually, this is done routinely with an oncologist, during their treatment, they get EKGs and if things are normal, then they are normal. There are specific parameters that are clearly laid out for those physicians about when it is safe to continue or not continue and then if there is ever a question about the EKG or just in general about the patient, then they will call us or ask us to come in and see the patient and evaluate, but usually those are pretty straight-forward for monitoring the EKG is pretty clear.

Hochester Can you, for the patients who get these drugs, can you tell us what problems they might run into or what the concerns are with the conduction?

Baldassarre The concern would be that if there was a prolongation of the QT that became too long, that could be a set up to have a cardiac arrhythmia, which would be an abnormal heart rhythm and that would usually present itself with things like feeling palpitations, like your heart is racing, feeling very lightheaded, like maybe you are going to pass out or even potentially passing out. Those would be the types of things to be concerned about if an arrhythmia was to occur.

Dr. Lauren Baldassarre is an Assistant Professor of Medicine and Cardiology at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer. You are on WNPR, Connecticut's public media source for news and ideas.