

Dr. Raymond Russell and Dr. Kerry Russell, Cardiac Side Effects of Chemotherapy September 15, 2010 Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening, I will be sitting in for Ed and Francine and my guests are Dr. Raymond and Kerry Russell. Raymond is an Associate Professor of Medicine and Diagnostic Radiology and Kerry is the Associate Professor of Medicine Cardiology at Yale School of Medicine and they are joining us this evening to talk about the side effects of chemotherapy on the heart. The Russell's are married, and I am assuming that it is probably relatively rare for a couple to share this interest. Raymond It is true actually. We did not get to know each other because of a longstanding interest in chemo cardio toxicity, but I guess the other way around. Both Kerry and I went to medical school together and graduate school, both those were down in Houston and we came up to New Haven to do residency and cardiology fellowships and stayed on faculty and since then have actually developed a strong interest in the side effects of chemotherapy on the heart. Barber Explain to me a little about what all of this involves. Kerry This is somewhat of an emerging field because of unanticipated side effects of newly developed drugs, and I had the good fortune of actually studying one of these drugs when I was a graduate student at MD Anderson Cancer Center in Houston. I had a longstanding interest in cancer biology and developing new strategies for treating cancer, and it was a very exciting time because people were really beginning to dissect out the molecular mechanisms by which cancers grow and I think people were very focussed on cancer itself and not on a lot of other organ systems that could potentially be affected. It turned out that this drug that was being developed, which is now called Herceptin and is very effective in the treatment of breast cancer, also has cardio toxic side effects. As I did additional training I ended up being very interested in cardiology in the clinical setting and everything was brought full circle when it turned out that this drug actually has side effects in the heart, and now my research labs have been studying the particular target of Herceptin in the heart and looking at can we develop strategies to A., Protect the heart from Herceptin cardio toxicity? Because it's a very effective cancer drug and B., Can we also target those molecules in the heart to treat patients with other forms of cardiac disease? Barber You obviously both had a background in science before you met, but let's go all the way back to early school, when was it that science became interesting to you? Raymond It's funny because we really did approach and come to it from different pathways. I have always wanted to be a doctor and so the clinical side of medicine was always of interest to me. In elementary school when you were asked what you want to be when you grow up, I wanted to be a3:42 into mp3 file <http://yalecancercenter.org/podcast/aug1510-cancer-answers-russells.mp3> doctor. So during high school and college that continued to develop and I

did not think that much about the research side of medicine until I got to medical school and actually worked with an absolutely fantastic cardiologist who was one of Hans Krebs' last graduate students. Hans Krebs won a Nobel Prize for his work in metabolism. The lab was very interested in cardiac metabolism, and I just became fascinated with some of the aspects of that and the translational research aspects of how you can take what you learn at the bench side and take it to the bed side and help patients. And then in graduate school I became very interested in the research aspects of cardiology and in heart research. Then when I first started my own lab I started looking at heart failure and was drawn to the affects of one of the other chemotherapeutic agents, doxorubicin or Adriamycin, and its affect on heart function, which now for over 40 years has been known to have cardiotoxic affects, and this was just heightened by the fact that my clinical expertise is in nuclear cardiology, where we look at heart function with a test called an ERNA or a MUGA scan and so every day that I would read out studies, at least two or three studies would be of patients that were undergoing chemotherapy in which we were evaluating their heart function. I really saw my clinical interest and my research interest coming to a focus and that's been very exciting to now look at the mechanisms that are responsible for that cardio toxicity and try to identify both pathways that may be cardio protective as well as the pathway that are responsible for that damage.Barber How about you Kerry? What was the thing that got you interested in the science aspect?Kerry Actually, I had a high school biology teacher who took us on a field trip to MD Anderson. I grew up in Houston and we visited a breast cancer imaging lab and I was so completely turned on by the idea that you could apply science and math to learning about human disease and so I wanted to be a scientist. I had no concept of what a doctor did. My whole family is artists and musicians and I would like to say, I was the talentless one, so I did something else. Science and math were always interesting and easy for me and when I put that together with the idea that you could apply that in such a helpful way to patient care, which is what caught me and made me decide to go to medical school.Barber Although there really is very much an art to math and science is there not?Kerry Yeah, I think that's true. That is something that you don't get when you are kid and comes with maturity, and certainly medicine is almost more of an art than a science.Barber With this background and this expertise tell me what's going on in the lab?Raymond When you do research, it's really informed both by your past experiences and hypothesis as well as work other people do, and you take information from journals, from meetings you have been to, and discussions in the hallways and use those to then say for example, I wonder if this particular7:50 into mp3 file <http://yalecancercenter.org/podcast/aug1510-cancer-answers-russells.mp3>protein may play a role in protecting the heart against cardio toxicity. And your inspiration can come from the most unusual place and you may not have expected that you would put these two very desperate pieces of information together and come up with a hypothesis and then follow that out. You come up with your hypothesis and you try to figure out the best way to examine it and that might be either in isolated cells maybe

using animal models and then eventually if those prove to be positive studies, then beginning to explore the questions in patients. Barber Kerry, you referred to this earlier, with chemotherapy you are obviously trying to kill the cancer cells while doing as little damage as possible to the healthy cells, and you also referred to the fact that there are these great new drugs. What is the process by which you identify, as Raymond has said, something that is an area of interest and then focusing on it? Kerry In some cases, like for the story of Herceptin, I think that it was purely an accident and I don't think people had any idea that this was going to have cardiac side effects and that was purely through observation in clinical trials that people recognized patients were developing changes in their heart function, but I think that has opened our eyes to being a lot more careful about the potential cardiac side effects of newly developed drugs and that was the impetus for developing cross talks between the oncology community and the cardiology community so that we can be aware of potential cardiac risk factors for these drugs and we can also learn about the drugs that they are using which we're largely unfamiliar with as a group and help them develop ways of protecting the heart, and also use that information, as I eluded to earlier, to develop new treatments that are directed at heart failure patients independent of those receiving chemotherapy. Barber To what extent is it important for patients to be aware of the things we are speaking about today and what role does the physician, the oncologist play? Raymond It's very important to give a patient as much information as possible about what their therapy is going to involve and what they can expect from it. We do that every day when we are talking to patients with heart conditions who don't have cancer, but I think it is especially true when you then add on chemotherapy in which there are risks of developing heart failure. I think the oncologists, certainly here at Yale and at Smilow are very good about letting patients know what to expect. Unfortunately, with respect to heart failure, there are some fairly non specific symptoms that people can develop that can be purely because of the chemotherapy but not because of effects on the heart. Fatigue and shortness of breath are two very common side effects from some of the intensive chemotherapy regimens and those can also be seen in heart failure and so it is very important for patients to let their physicians know what sort of symptoms they are having, how they are tolerating chemotherapy, and then the oncologist who is certainly aware of those side effects and can, when necessary, talk to the patient and to a cardiologist about further evaluation. 12: 11 into mp3 file <http://yalecancercenter.org/podcast/aug1510-cancer-answers-russells.mp3> for those patients. Barber You are very busy aren't you? What I found very interesting about this and it is great for you to spend the time because I know how busy all of you are. How do you manage the two important ways you can allocate your time, which would be one, the treatment of patients and two, the research into the science? Kerry I will say that we wear a lot of hats. There is a lot of juggling and the good thing about it is that each aspect has its own rewards and its own frustrations. The research lab is a place where you can spend that quality intensive cognitive time reasoning through questions

but it has its own frustrations and you have to write grants and write papers and subject yourself constantly to critique from colleagues and you can go very slowly and you can put a lot of effort into something that never really pays off. On the other hand, patient care is something that always happens and there is always the reward of working with people, which is fantastic, but that has its own frustrations as well, dealing with insurance companies and those kinds of issues. I enjoy going back and forth. I think most people, in order to have success in both areas, have to choose slightly one over the other and one of the nice things about having a focused area is that you can stay up to date with it and be a leader in the field as opposed to being in general cardiology. Barber We are speaking with Drs. Raymond Russell and Kerry Russell, husband and wife. We are going to take a short break and we will be back. We will talk about some of the things that are on the horizon both in your practice of medicine and also in the field in general. 15:24 into mp3 file <http://yalecancercenter.org/podcast/aug1510-cancer-answers-russells.mp3> Barber We are speaking with Drs. Raymond and Kerry Russell about cardiac chemo toxicities. When we left off we were talking about a lot of the science and what has been going on in that aspect. I want to now look forward into something that sounds very exciting and is something that you are working on, which is a specialty care program. Tell me a little about that. Kerry This is, as I mentioned, a newly emerging field and at most cancer centers now they are developing the need for some sub-specialty care in this area, and with the opening of the new Smilow Cancer Center we are very excited to start a program in this area of specialization here at Yale. There actually are two national meetings going on this year at other cancer centers, one at Vanderbilt and one at MD Anderson. As a group cardiologists around the country are establishing these programs and it is a chance for us to all grow and learn and give much better care to patients as far as their heart goes in the setting of chemotherapy, because with the new chemotherapeutic agents we expect people to live much longer lives and we want to make sure their heart stays healthy to enjoy that. Barber That is an interesting thing that is happening, we solve these problems and people are living longer, but then you do have problems associated with that. Raymond Absolutely, and I think it's especially true in patients who had childhood cancers and very fortunately they are living to ripe old ages, and long-term effects of their chemotherapy may start affecting their heart, or they will have had the chance to develop garden variety coronary artery disease, and so I think the ability to interact with the oncologist and provide specialty care for patients who have cancer, not only to deal with the affects of their chemotherapy, the affects on heart function, but then also to help inpatients who have coexisting coronary artery disease and cancer, or to help evaluate patients for specialized therapy in which there may be increased risks to the heart muscle. This will be very important and is an area that we are very excited about contributing to. Barber Is that something you have got to tease out, whether the heart problem was related to the chemotherapy or to something that was preexisting? Kerry At this point, we do not have refined treatments specifically for a lot of these

cardio toxicities. I think there is another really important thing that we as a national and international community of cardiologists and oncologists need to develop which are collaborations and multicenter trials, because right now we treat every heart failure pretty much the same and for many of the newer drugs we don't really have a great idea of what the mechanism of the toxicity is or any of those kinds of things. It's a moving target in a way and there have been only a few trials so far looking at traditional cardio protective drugs that we used for lots of other kinds of heart failure in patients19:03 into mp3 file <http://yalecancercenter.org/podcast/aug1510-cancer-answers-russells.mp3>undergoing chemotherapy. It's a chance for us to develop new strategies and I would say at this point we don't have fine tools for dissecting out in a patient what the cause of the cardiac complication is so we are not to that fine of a level yet, but hopefully in the future we can develop specific strategies for treating this side effect.Barber You mentioned the fact that there are these meetings where it's a collaborative environment to get a bunch of people together to talk about these issues.Raymond Yes, as Kerry mentioned it's a very young field, and so everybody is going at it with a lot of enthusiasm to get together the oncologists and cardiologists and identify what the problems are from both sides so that we have a common vocabulary to understand what the issues are and to identify what tests are at our disposal to help identify what the etiology of a particular heart problem might be in a patient who has cancer and is undergoing chemotherapy. But then also to collaborate in a multicenter way to learn more about these complications and help us identify biomarkers, blood tests, or noninvasive imaging techniques, or even genetic tests that might help us identify patients that are at risk for some of these cardio toxicities. I think that these are some of the things on the horizon that are very exciting in this very early stage of the field.Barber You mentioned clinical trials briefly earlier, is that something that's important for patients to express an interest in participating in?Kerry Yeah, and again, with the opening of Smilow, I think we are going to have a lot of patients that will be on trial drugs for their cancer treatment, and I think that we need to have our eyes open and get those patients help in trying to detect any potential cardio toxicity for these new drugs.Barber In the science part, I would imagine that it becomes very exciting to have better records and more done with digital technology and the ability to share information and collaborate?Raymond Absolutely, an important aspect of research is having reliable accurate reproducible data, and in the lab that is fairly easy to do. When you go into the clinical setting, there are so many more variables that enter into it and being able to accurately track a patient to get data from a patient's chart in a reliable and somewhat easy manner, rather than flipping through 300 pages of handwritten charts, is a big help. And like most physicians, we have horrible handwriting, so that can just double the amount of time it takes, so having electronic medical records is very important and really helps with identifying complications, of identifying patients that we can learn a great deal from.Barber What is some of the research that is emerging right now that's most exciting to you?22:47 into mp3 file [5](http://yalecancercenter.org/podcast/aug1510-cancer-answers-</a></p></div><div data-bbox=)

russells.mp3 Kerry There are two ways to answer that. The first is from a clinical standpoint, we have newer technologies to try to dissect out cardiac dysfunction in an earlier and more sensitive way and I think some of that is going to allow us to pick up on small changes in cardiac function before they become severe, and those are primarily imaging modalities like specialty cardiac ultrasound which is one the things that I work in and other types of cardiac imaging like cardiac CT and cardiac MRI, so the imaging field has really taken leaps and bounds forward, and I think that's a very exciting area. From the basic science standpoint, we have a lot of newer types of genetic models of human disease that allow us to hopefully pre-test some of these agents for cardio toxicity, and people are a lot more aware of this so hopefully in preclinical testing some of these drugs will undergo more rigorous screening and help us to identify potential toxicities before they occur in clinic. Barber Not to send everybody out to the imaging facility, but would it help you to have baseline stuff? Raymond Yeah, so before someone starts chemotherapy it's a standard of care to assess the heart's function, left ventricular function, either through a nuclear scan that I mentioned before, a MUGA, or through a cardiac ultrasound to identify whether or not someone has baseline heart dysfunction, and if that's the case, that would be the sort of person we would see even before they start chemotherapy to help make decisions of how they can optimize their treatment, but at the very least to establish what their baseline function is. In addition, if patients have any sort of concern about coronary artery disease either because of the presence of chest pain or multiple risk factors for coronary disease, that sort of patient may benefit from having a stress test to help identify what we call their risk of having a heart attack in the future, and that can allow us to initiate therapy once again to help protect the heart in the setting of continuing chemotherapy. Barber Let's talk a little about once you realize there is chemo toxicity, what's the process? How do you treat that? Kerry Because, as I said, we don't have very fine tools at this point, there is big discussion that needs to go on between the patient, oncologist, and cardiologist about what the relative benefits are. In many cases, we have good therapies for treating mild heart failure and in many cases we can deal with the heart problem in favor of treating in cancer if the cancer is responding to the chemotherapeutic drug. In some cases we will have to collaborate with the oncologist to change the chemotherapy to something that's less cardio toxic. So far, in my experience, many times we can make it through in favor of being able to use these very potent drugs to treat the cancer. So it's really an important collaboration. As you pointed out earlier, we are trying to kill the cancer without killing the rest of the patient, and I think that an informed discussion about the relative risk and benefits of the therapies with the knowledge that often we can treat mild heart failure very26:59 into mp3 file <http://yalecancercenter.org/podcast/aug1510-cancer-answers-russells.mp3> effectively to get the patient through and be able to be cured from their cancer, those kinds of discussions are very important. Barber Are there preventive measures to take when you are aware of these risks? Raymond There are, one is actually fairly straight forward, not necessarily always simple, but

fairly straight forward, and that is to have a healthy lifestyle in the setting of your ongoing therapy. There have been studies that have demonstrated a cardio protective effect against the chemotherapeutic agents by exercise, and so that's something that is obviously good for everybody anyway, but can certainly help protect against some of the effects of these chemotherapeutic agents. In addition, there have been small studies that demonstrate certain medications that may help protect the heart, and these should be considered I think in patients that are certainly at higher risk for developing cardio toxicity, but the studies tend to be fairly small and they have not been overwhelmingly conclusive to the point where we would say absolutely everybody on this particular chemotherapeutic agent should get this drug to help protect their heart. Barber It sounds like we are getting somewhere with this and that this field has just started to develop and it must be really a very exciting time for both of you. Kerry Yeah. Raymond It absolutely is. It is great to have the intellectual collaboration with the oncologists and obviously, taking care of patients is why we got into medicine, and so helping a patient deal with what can be a very devastating disease is quite rewarding. Barber My thanks to Drs. Raymond and Kerry Russell for being with us this week on Yale Cancer Center Answers. If you have questions or would like to share your comments, visit [yalecancecenter.org](http://yalecancecenter.org) where you can also subscribe to our pod cast and find written transcription of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.