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## Advances and Clinical Trials for Sarcomas

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*Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week it is a conversation about sarcomas with Dr. Hari Deshpande. Dr. Deshpande is an Associate Professor of Medicine and Medical Oncology at Yale School of Medicine, and Dr. Gore is a Professor of Internal Medicine and Hematology at Yale and Director of Hematologic Malignancies at Smilow Cancer Hospital.*

Gore I do not think many lay people have ever heard of sarcomas?

Deshpande I think you probably would be correct. They are very rare compared to cancers that other people treat. I will just give you a couple of numbers – we see over 1.5 million cancers a year that include the leukemias, the lymphomas that you see but also cancers like lung cancer, breast cancer, prostate cancer that most people have heard of, and they account for something like 1 million cases. Sarcomas on the other hand, we only see 15,000 cases across the whole country and we split those into 2 main types.

Gore Wow. So, those more common cancers that people are familiar with like lung cancer and breast cancer, those are called carcinomas, right?

Deshpande That is correct, yes.

Gore What constitutes a sarcoma, and in what way is the sarcoma different than a carcinoma?

Deshpande Sarcomas are cancers of what we call mesenchymal tissues. We like to give everything a long name to make it sound more intelligent.

Gore Exactly, you have earned your paycheck in some way, right?

Deshpande This is basically cancers of bone, muscle, tendons, even fats.

Gore Connective tissue?

Deshpande That is correct, yes.

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Gore And is that fundamentally different than cancers of gland tissues that most of the other ones are?

Deshpande It does seem as though it is. They do not tend to respond the same way to the same kind of treatment.

Gore Sarcomas, connective tissue cancers if you will, and you mentioned a bunch of tissues, you mentioned bone, and you mentioned tendons I think and cartilage I guess would be among them. Does each one have its own sarcoma?

Deshpande We split them broadly into 2 main types. We have sarcomas of the bone in one category and then everything else we call sarcomas of soft tissue. Now, the bone does include cartilage.

Gore Which is semi soft?

Deshpande Exactly right.

Gore Gotcha. Why is that distinction put in place?

Deshpande Mainly because of the treatment option. Bone or osteosarcomas are treated mainly with chemotherapy and surgery, and they are very chemo-sensitive, especially the osteosarcomas. Whereas with the soft tissue sarcoma, surgery and radiation are the main treatments. We sometimes give chemo but it is a little less sensitive as a group.

Gore So, biologically it sounds like they really are different?

Deshpande That's correct.

Gore And we do not have any idea why that is?

Deshpande No, I know there are a lot of very clever people who have done research into it and hopefully we will get more information.

Gore But so far, no real thoughts that way.

Deshpande No.

Gore It sounds scary, I guess some of these sarcomas of the bone might present in bones that are really important like bones that help us walk or use our arms or something like that?

Deshpande Yes and that is one of the problems with this disease. Whether it is bone or soft tissue, they can occur in bones like your arms or your legs where I know I get joint pains all the time and just say nothing and unfortunately by the time people have a sarcoma that is found, it is often has progressed quite far.

Gore And so, some of those people might require amputations?

Deshpande I think the surgeons are the best people to talk about that and they will tell you that over the years, they have been moving away from amputations. So, wherever possible, they will try and do something called a limb-sparing surgery. Now, most sarcomas, if not all of them, if the surgeon is going to try and remove them, they do what we call a wide margin; in other words, if you see someone who has a sarcoma and you say, well I saw the actual lump and it was only as big as my hand but the operation they did was twice as big as that and that is because they have to make sure they get all of the sarcoma out plus some normal tissue around it. Now, if it is possible to do that without an amputation, then they will do it. But if it involves the joints, then sometimes they have to do an amputation.

Gore I remember well when I was a kid growing up, Ted Kennedy's son, Ted Kennedy Jr., as I recall, had an osteosarcoma. I assume it was an osteosarcoma and it was quite big news.

Deshpande That is correct. He was diagnosed and treated in Boston, and he got the standard treatment, which is chemotherapy, then surgery, then more chemotherapy and luckily, he has done very well.

Gore And he is a great leader in our state.

Deshpande Yes that is correct.

Gore That is really a happy story and I do not think we are divulging any confidence because this was national news.

Deshpande Right.

Gore And that was back, I am thinking, in rather the primitive days of oncology. I am guessing, I feel like I was teenager at best when that happened.

Deshpande I think it was the 1980s or maybe the 70s, but unfortunately, in one way you are correct because the treatment has really not changed very much since then as we use the same medicines, methotrexate, doxorubicin and cisplatin that we used back then.

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Gore Those are chemotherapy drugs?

Deshpande That's correct, yes intravenous chemotherapies.

Gore And so, he was a kid or a teenager as I recall at that time. Is that common?

Deshpande Osteosarcoma and other bone sarcomas like this cancer called the Ewing's sarcoma are mainly cancers of childhood. But we do see them up until around the age of 50. So, they can occur in adults, but typically in children, yes.

Gore And is that true also of the soft tissue sarcomas that you spoke about?

Deshpande No, they have more of a variation. I mentioned soft tissue sarcomas, there are actually 50 different subtypes and that is why it is so hard for fellows to learn, those are the training doctors who we train at Yale, because not only is it a rare cancer to start off with, there are 50 different types.

Gore 50 out of 15,000 right?

Deshpande Exactly. Well, actually 50 out of 12,000 because 3000 of the bone and 12,000 of soft tissues.

Gore I hope our audience is keeping a score card.

Deshpande But some of them, like rhabdomyosarcoma, are mainly in children.

Gore You are just saying these things because they are complicated, and they make you sound smart.

Deshpande I have been practicing very hard on it.

Gore So that is a muscle cancer.

Deshpande That's correct, and then there are other ones, there is one that we call undifferentiated, in other words, we cannot put in an actual category, but that is much more common in older adults over the age of 50.

Gore I can imagine that if you have 50 subtypes and just so I can do the math in my head, let us take it out of 15,000, so is that about 300 of each type per year?

Deshpande It would be if they were equally distributed. So, we do see some more than others, but those are the sort of numbers that we are talking about.

Gore It must be very hard to study such individually rare cancers and really try to figure them out, assuming that they have significant differences that overwhelm their similarities biologically?

Deshpande I think that is the big problem over the years in trying to get a standard treatment for all these cancers. We have tended to lump all of them together and study. And so, if you look at some, especially the older sarcoma studies, they are very heterogenous, in other words, they have lots of different types and so people will criticize those studies to say, well, it was not just one type of soft tissue, it was many different types and you cannot get a good decision from a study like that.

Gore Of the 6 syllable words that we used, heterogenous I think is probably okay. So, that is challenging and of course I am sure there are many centers just speaking of the referral centers, never mind community oncology centers, but there are many centers among which these 300 or so cases of each disease get distributed, so even the biggest centers like say Memorial Sloan Kettering or MD Anderson must not have so many in one place.

Deshpande Yes, that's true and we really have to work together.

Gore That is anathema to academic physicians isn't it?

Deshpande It is difficult but I think it is something that we have to.

Gore Anathema by the way has 5 syllables, I am guilty as well. So, how do you do that? Do you just sort of send out a kumbaya e-mail and say, hey I think we all need to work together?

Deshpande There are a few mechanisms. Sometimes if a medicine looks very promising, then the company that makes that medication will choose sites all over the country, sometimes all over the world, to run a trial, one example of that was a trial that was actually run by Sloan Kettering physicians, Dr. William Tap at Sloan Kettering, and it was the first time that any medication had proven to be better than our standard treatment for probably over 30 years and that was a medicine again with a long name, olaratumab.

Gore That's bad.

Deshpande Yeah, that is a bad one, but it is a good medication. It seems to be very promising, it is still not quite accepted as the standard, but it is showing a lot of promise in combination with standard chemotherapy.

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Gore So it is not used by itself?

Deshpande No, it has to be used with chemotherapy.

Gore And if I have got my hat on correctly because you said it ended in a -mab, this must be some kind of antibody drug?

Deshpande That's correct, it is an antibody against something that people feel is very important in some sarcomas, called PDGFR-alpha.

Gore That is a receptor for growth factors?

Deshpande That is correct, yes.

Gore And that is important in sarcomas?

Deshpande It seems to be, and it was a trial that had sarcomas not just one of the 50 types but any of the 50 types could have been included in that particular trial. When I say any, there are a couple of exceptions.

Gore And what kind of results were found with that?

Deshpande What they found was that, normally when you treat people with what we call metastatic sarcoma or stage IV sarcomas, the average survival is just over a year usually, which is not very good and something we always try to improve on. When they gave people their chemotherapy plus the antibody, then the survival went up to 26 months.

Gore Oh! That's quite a big difference.

Deshpande It was a very big difference, and this is what we call a phase II trial, and I know you are familiar with that, but basically it is not a trial that is a definitive, this is better than that trial, and you always have to do a phase III to confirm those numbers, and that is being done as we speak.

Gore I see. And was it hard to get all these hospitals and physicians to work together?

Deshpande Yale was not part of that particular study, but I looked at the journal where it was published, and I was amazed at the cooperation that everyone had in doing this particular trial that was completed very quickly, so I think people were very focused on getting patients on that particular trial.

Gore I see. And is this drug FDA approved now or that is still awaiting the phase III trial?

Deshpande No, the results were so compelling, the FDA approved it, but with a condition that if the phase III was not positive, then they may have to withdraw it.

Gore That is really fascinating to hear such important progress, which we hear, unfortunately too infrequently. Right now, we are going to have to take a short break for a medical minute. Please stay tuned to learn more about advances in clinical trials for sarcomas with Dr. Hari Deshpande.

### *Medical Minute*

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*This is a medical minute about genetic testing, which can be useful for people with certain types of cancer that seem to run in their families. Patients that are considered at risk, receive genetic counseling and testing so informed medical decisions can be based on their own personal risk assessment. Resources for genetic counseling and testing are available at federally designated comprehensive cancer centers. Interdisciplinary teams include geneticists, genetic counselors, physicians and nurses, who work together to provide risk assessment and steps to prevent the development of cancer. More information is available at [YaleCancerCenter.org](http://YaleCancerCenter.org). You are listening to Connecticut Public Radio.*

Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore. I am joined tonight by my guest Dr. Hari Deshpande. We have been discussing a group of cancers known as sarcomas. Hari, that was a really fascinating story you told prior to the break about this antibody drug that really has made a remarkable difference, it seems at least in preliminary data, it has been a remarkable difference. I know that in many of these clinical trials, research studies, the statistics are driven by improving the average length that people with one treatment or another survive, and of course, that is important and then you get statistics like well it is a 50% improvement in survival, and it sounds great to patients, but it sometimes neglects the dirty little secret that in many studies, nobody is cured forever or that there are very few people who are long-term survivors, so do we have any sense for this kind of drug, whether it is improving the number of people who are in remission long-term?

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Deshpande I haven't seen the very long-term data, but the data I have seen suggests that it is still not a cure for the disease. The curve seems to be dropping down at the end and it is unfortunate.

Gore I do not mean to be Debbie Downer, but I think it is important and patients do not always get the whole picture. No doubt an average survival of what you say 9 months to 20-something months.

Deshpande It was about 14 to 26.

Gore I mean, that is incredible, and I would sign up for that for sure. And I guess some of our listeners may have known people who have been treated with other kinds of antibodies, I know there is a Herceptin drug for breast cancer and a variety of drugs that are used for lung cancer along those lines that have also made a very remarkable impact, I think, on some of those diseases.

Deshpande Definitely, yes.

Gore This is exciting and the other area of course that we hear a lot about these days and particularly in some of the more common carcinomas are these immune modulating drugs, which have really changed things for a lot of people, anything going on there with sarcomas?

Deshpande There have been some trials. Most of them are pretty small trials. There are a couple that were reported at ASCO, that is our annual meeting where many of the trials that are being done all over the world are presented, and there were two that looked at different immune therapies, one was pembrolizumab, that is a single antibody against one of the proteins that people feel is important in the immune system attacking cancers, and the other one was using a combination of two of those types of medicines, ipilimumab and nivolumab; and both of them seem to suggest that some sarcomas may respond better than others. Now, remember these are trials that have maybe 10 people with each sarcoma.

Gore So probably they are advanced cancers usually?

Deshpande Exactly, and it is hard to really say these are definitive trials, but I think the results were compelling enough that one of the types I mentioned, the pleomorphic or undifferentiated sarcomas, that is the type we see most in older patients. And so, those I think have the best chance of responding to immunotherapy.

Gore Well glimmers of hope are always important, and as a clinical researcher, I hear a

glimmer of hope like that and I am already starting to think about the next trial where let us put that together with your anti-receptor drug and your chemo or something like that. I am sure I am not unique in thinking that way.

Deshpande No, I think that is how many people are thinking.

Gore Hari, let us get back to this kind of group think and the group strategizing. Before the show, if I understood correctly, you were telling me that there is some kind of new group forming for sarcomas?

Deshpande Yes, it is not that new actually.

Gore It seems like just yesterday to me.

Deshpande It does.

Gore Remember Y2K?

Deshpande I remember it well. I even have a tie to commemorate that. They actually called it tie2K.

Gore And we both survived.

Deshpande Yes. But just after that, 5 big cancer centers got together and formed this group. They called it SARC, and it has gone from strength to strength. I was very interested in joining this group and so we joined as an institution 2 years ago now and we have our first trial with them opening hopefully soon. There is a lot of red tape as you know in opening trials, and it has taken a little while, but that is for one very rare type of sarcoma that hopefully will be opening a trial here.

Gore How does this work? You have a variety of groups, is it 6 now or are there many more?

Deshpande There are many more now.

Gore In the SARC?

Deshpande Yes.

Gore So, a group of institutions working together?

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Deshpande Right. And what they do in their head office, I think in Michigan, I may be wrong about that but they will get together with the board of directors and say we have enough funding to open this trial in say 5 places or 6, and they will choose institutions that are interested in it and open it in those particular institutions.

Gore But who comes up with the ideas and what is the governance out of choosing which is the best idea?

Deshpande Well, to be honest with you, any of the members can come up with ideas and of course it has to be vetted by the people who are involved in the SARC administration, but they are a very nice group to work with.

Gore That's great and how is such a group funded?

Deshpande That is a good question. I know they do get philanthropic funds, but that is something I did not look at before the show.

Gore I am just curious because our listeners probably do not know but the National Cancer Institute funds many large interactive groups like this, they tend to go by regional names like the Eastern Cooperative Oncology Group or the South-Western Oncology Group which is kind of always funny because many of the centers like Yale are in the South-Western group and Stanford happens to be in the Eastern Cooperative Oncology Group, and those get federal funding primarily.

Deshpande Right, and actually I do know that SARC got what they call a SPORE grant for I think it was 12 million dollars over 5 years. Now, that was back in 2012. So they are just sort of coming to the end of that.

Gore And that was federal funding that was applied for?

Deshpande They must have, yes.

Gore That's great. And I also understand that you are a leader in setting standards for how sarcoma patients are to be treated?

Deshpande Yes, that is something called VIA pathways, and it is a program actually that is developed centrally for institutions to use, so Yale is one of the institutions that uses the VIA pathway, and I am one of the co-chairs for the sarcoma committee. Basically, what we do is we look through all the guidelines, as you know we have some national guidelines like ASCO and the National Cancer Network, NCCN, that will come up with

what is the best way to treat certain diseases, and sarcomas are no exception, but then when you are actually entering the electronic ordering system that we have all over the country, at Yale we use one called Epic, then there is no actual guidelines to say this is the actual medicine that you should use. So, what we are trying to do is make it a little easier for physicians to choose what is the medication with the best evidence behind it. Now, that obviously has its problems, everyone is different, every patient is different, so sometimes you may want to stray away from the guidelines, but if you do, you have to have a reason for why you did not follow what is considered the best evidence.

Gore And we all know that the evidence that we use to come up with such guidelines is not always as strong as some other evidence.

Deshpande Exactly, and I think that is why when we make these guidelines, and I was just at the committee meeting which is a webcast that we all sign into, you would be surprised how much debate there was over every single decision that we made. It just goes to show that you have got some very smart doctors out there treating sarcomas who know the data very, very well and will really insist on finding the best treatment for their patients.

Gore It really does not surprise me. I have served on such similar committees in leukemias and you know people are very passionate and people who are leaders in academic institutions are very passionate and I find that many people can look at the same data and feel very differently about it.

Deshpande That is exactly the discussion that was held, yes.

Gore If the data agrees with my opinion, then it is a great study, and if it does not agree with my opinion, well maybe there are problems with that study, although we are all seeking truth, right?

Deshpande Right, and I think as long as we do not feel it is a bad decision, I think it is something that we can put on the pathway and that is the way I was trying to chair that discussion.

Gore That's great, but at the end of the day who chooses the pathway? We have physicians in our network and they are treating patients with various cancers and in your case sarcomas and they chose something on or off the pathway, I think it is great that they are getting advice from the pathway, am I right? Are there any consequences of being on the pathway and not being on the pathway for the physician and for the patient?

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Deshpande As an institution, Yale for instance, we are expected to use the pathway for the majority of our chemotherapy orderings. I think it is over 80% has to be on the pathway. So, I chair the meeting with Dr. Chau from the City of Hope. It is nice to have a meeting where we can bring the two coasts together.

Gore Especially if we could travel to California.

Deshpande Unfortunately, it was a telephone call.

Gore It is a beautiful campus in City of Hope, it is near Pasadena.

Deshpande But, what happens is if we do not use the pathway, then VIA has metrics where they will say okay 50% of the people for synovial sarcoma, which is one of the types that did not use the pathway, maybe we should change the pathway. So, if people are just not using it because they are too lazy, that is one thing, but if they are not using it because there is a good reason, then I think it means that we have to change it.

Gore I think that is really interesting because if you are using the pathways to reinvent the pathways and to seek kind of a better standard of care it sounds like, that is very appealing. If you are punished because you are going off the pathway for some reason, then I wonder how that is being helpful.

Deshpande Well, I think there is that side of it, so I think insurers and Medicare will look at these pathways and say unless institutions are using best evidence, then we may not give the same benefits to those institutions as the ones that do use those. So, I am not part of the economic side of it, but I am sure that is part of it.

*Dr. Hari Deshpande is an Associate Professor of Medicine and Medical Oncology at Yale School of Medicine. If you have questions, the address is [canceranswers@yale.edu](mailto:canceranswers@yale.edu), and past editions of the program are available in audio and written form at [YaleCancerCenter.org](http://YaleCancerCenter.org). I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on Connecticut Public Radio.*