

Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at the Yale Cancer Center, Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about stem cell transplantation with Dr. Stuart Seropian. Dr. Seropian is an Associate Professor of Medicine and Hematology at Yale School of Medicine. Here is Dr. Steven Gore. Gore Why don't you tell us what is a stem cell transplant? Seropian There are a couple of different types, I am sure we will get into that but the basic idea is to use hematopoietic stem cells. Gore Hematopoietic? Seropian Yes, these are cells that help make blood, so they are not embryonic stem cells that we hear a lot of news and controversy about. This is not a controversial subject. These are stem cells that help to make blood and we use them in cancer therapy to support the administration of chemotherapy and sometimes also trying to give people a new immune system to try and fight cancer. Gore So you are telling me that there are two functions of stem cells? How do stem cells support chemotherapy? I do not understand that. Seropian A lot of cancers of the blood or immune system are curable with systemic chemotherapy but not all cancers, so a good example is acute myeloid leukemia in older patients, it is very hard to cure with standard chemotherapy. Some of these cancers may be curative if we give very high doses of chemotherapy, but then the blood counts will get very low, the patients will get very sick and sometimes it is not possible to do that. If we have a source of healthy stem cells that can make blood we can use them after the administration of high doses of chemotherapy to make the administration of the high dose chemo safer. Gore So in other words, if you just gave the high dose chemo, people's blood counts would take a long time to recover and they might get sick or die, but the new stem cells, do what? Seropian This is really a blood therapy. Lots of people sometimes hear transplant and think that maybe surgery involved. This is really transfusion therapy where stem cells may be obtained from a patient or may be from a donor and they are administered like a transfusion and they will go through the blood to the bone marrow and they will just start making stem cells the way our blood stem cells do ordinarily throughout life. 2:55 into mp3 file <http://yalecancercenter.org/podcasts/2014%200427%20YCC%20Answers%20-%20Dr%20Carlson.mp3> Gore Fascinating, so you mentioned that there are different sources of stem cells, can you go into that a little more? Different as to where the stem cells come from? Whether it is the patient or a donor? Seropian Absolutely. Take for instance a disease like non-Hodgkin's lymphoma, we can collect the stem cells from the patient, we are using their own stem cells, now-a-days we harvest them out of the bloodstream through a process of filtering the blood called pheresis and they can be frozen and

then they are thawed out and administered to the patient after we give a high dose of chemotherapy for the purpose of having a faster recovery of the blood counts to make the procedure safer. We can get similar cells out of the bone marrow, which is what a bone marrow transplant is, although if we are using the patient's own cells, we tend to get more cells if we collect them out of the blood. That would be called a peripheral blood stem cell transplant. For certain diseases that works well, for other diseases it does not quite work as well because we need more than just the high dose chemotherapy to try and cure the disease. That is when we might consider a sibling as a donor of the stem cells or even an unrelated volunteer and there are some new sources of stem cells like umbilical cord blood. So those are more complicated transplants that require a donor and we really are replacing the immune system. We think of that like an organ transplant like someone needing a new kidney or a new heart, but as I mentioned before, there is the added benefit of a new immune system to fight the cancer as well. Gore

Well I definitely want to talk to you more about that, but just to finish up on this high dose therapy where people are giving their own stem cells to help them recover better, are you not worried about giving them back their cancer cells? How does that work? Seropian

There is a concern and in fact there has been a lot of research over the years to try reduce the risk of that, so a simple way to try and reduce the risk of that is to collect the stem cells at a time when the patient has been treated and they have already gone into a good remission and in fact those are the situations where using the patient's cells and giving the high dose chemotherapy is most likely to work. So we are giving the patient treatment to get them into a remission and often this is for a patient that has relapsed so we are getting them into a second remission, and then we collect the stem cells at a time where there really is very little disease left in the body and the high dose chemotherapy is to try and eradicate that small amount of stubborn disease that is left and in most cases, in a disease like lymphoma or Hodgkin's disease for example, the tumor cell contamination, which is what we call it, is minimal. There are diseases like multiple myeloma where we probably do collect some tumor cells whether they survive the freezing process is uncertain, but they do not appear to contribute to relapse in a material way. Gore

So are these transplants where people are getting their own stem cells back delivered with the intent of curing the patient or just giving them a remission? Seropian

It depends on the disease. In a disease like relapsed Hodgkin's disease or non-Hodgkin's lymphoma like a large cell lymphoma, which is the most common kind of lymphoma, we are 6:29 into mp3 file <http://yalecancercenter.org/podcasts/2014%200427%20YCC%20Answers%20-%20Dr%20Carlson.mp3> doing that procedure with curative intent. When we use the patient's own stem cells, this is in general a safer procedure. There are not as many expected complications, so there are other diseases like multiple myeloma where we do not think we are going to cure the patient, but many patients benefit in terms of a better remission or longer remission and it has a place in their therapy along with other agents we use to treat that disease. Gore

Very interesting. Why would I want a new immune

system? Why would that be helpful to me? Seropian Well transplantation started in the late 60s and 70s with the idea of giving high dose chemotherapy, as we were just discussing, and in the cases where transplants were performed with the donor it became evident later on in the 80s and 90s in particular that the immune system that we are transferring to the recipient is helping to fight the cancer and we know that high dose chemotherapy can help some patients, but it does not help as much in certain diseases, particularly if they are not responding well to standard chemotherapy. So diseases like acute myeloid leukemia, we think there is an extra benefit of a donor's immune system fighting the cancer and in fact we know pretty confidently from clinical experiments like giving extra immune cells from a donor after a transplant to treat recurrent disease, that the immune system really can help to fight lots of different malignancies, so that would be a reason, if one feels like the high dose chemotherapy is not going to eradicate cancer, then we might turn to a donor where we get the added benefit of the immune system to help try to improve the cure rate. Gore So, would not everybody who has one of these hard to treat diseases automatically, if they had a donor, want to get something like that? It seems like I would want that extra immune boost to try to cure my leukemia no matter what. Seropian That is right. In a perfect world if we could do those types of transplants with the same level of low risk as transplants using the patient's own cells, we probably would do that, giving a new immune system is a more complicated procedure. It carries some extra risks that we do not have to worry about with an autologous transplant and the main one is an illness called graft-versus-host disease. Gore Just to remind everybody, the autologous transplant, that is the one where you get your own cells? Seropian That is right. Gore And what do you call the one with other stem cells? Seropian That is called an allogeneic transplant. Gore Allogeneic transplant, is somebody else's stem cells. 9:23 into mp3 file <http://yalecancercenter.org/podcasts/2014%200427%20YCC%20Answers%20-%20Dr%20Carlson.mp3> Seropian So a sibling, a brother or sister, an unrelated volunteer donor, or a cord blood transplant are coming from another individual, a family member maybe who is not matched, sometimes we use that as a technique to try and get a new immune system. Any time these cells come from somebody else, that is an allogeneic transplant. Gore Stuart, maybe you could walk us through what happens to a patient who is undergoing one of these allogeneic transplants. I mean do they just come in and get infused with cells? Can you walk us through that? Seropian Sure, let's take a patient who has acute myeloid leukemia as that is one of the most common indications for an allogeneic transplant. These patients are always treated with chemotherapy at the time of diagnosis and then a determination is made if a transplant is necessary and that is made by their leukemia doctor in collaboration with a transplant physician. Some patients may have a transplant as a part of their initial therapy, some patients may have standard chemotherapy, and we hope they are cured and save a transplant for a later day, but if a transplant is indicated, a donor has to be identified so that is the

first step. There is a simple blood test, or sometimes we use a cotton swab in the mouth to test genes that govern how the immune systems relate to each other and we look for a match donor. Interestingly, you do not have to be the same blood type as your donor, it helps a little bit, but it is not crucial, and we do tissue typing called HLA type and we find a donor hopefully in the family but if not we look in the National Registry, we may look for a cord blood and once we have identified a donor and scheduled the time for the donor cells to be collected, then the patient will be scheduled to come into the hospital for a transplant. So, as a general outline, patients receive chemotherapy with and without radiation and that is usually administered over a period of as few as 4 days or up to 10 days and then the stem cells that have been collected from the donor are infused like a blood transfusion and there is a period where the blood counts are low, because the treatment we are giving is usually fairly intensive and we wait for the blood counts to recover. It is usually a period of about two weeks. Gore It takes that long for the stem cells to grow? Seropian That is right. So the blood counts will be low for that period of time because of the effects of the chemotherapy given or the radiation. Once the blood counts recover most people leave the hospital in 4 to 7 days and because we have given cells from a donor, where the immune system is different, special medicines need to be administered to make sure that part of the immune system from the donor does not make the patient sick, and that is this graft-versus-host disease we were speaking of. Gore But I thought you said the patients were a match and you are doing that cotton swab and stuff? Seropian The matching serves to allow us to do these types of procedures without a real risk of the patient rejecting the donor cells. So, there is a risk of rejecting donor cells if the patients do not 12:46 into mp3 file <http://yalecancercenter.org/podcasts/2014%200427%20YCC%20Answers%20-%20Dr%20Carlson.mp3> have the same genes, but unless you have an identical twin, the immune system between individuals vary greatly, even if they are matched for these major genes. There are lots of other genes that we know are different between everybody including people who are related to each other and if we tried to match every single gene that exists for this, we would never find an appropriate donor, if we were that strict. So, these are major genes that really govern the safety of the procedure, but we still need to use some method to control the donor's immune system for a period of time. Anyone who knows someone who had a kidney transplant or heart transplant knows that those recipients of an organ for another individual have to take rejection prophylaxis for their whole life, but that is not true of an allogeneic transplant when we are doing it for leukemia or other cancers of blood. Gore So, they do not need to stay on this anti-rejection drug forever? Seropian If drugs are being used, that is the method we are using to prevent this problem of graft-versus-host disease. Usually the patients are on those medicines for 4 to 6 months and then we try to remove them. Some people do have to take them for a longer period of time. Gore That is fascinating. We are going to take a short break for medical minute. Please stay tuned to learn more about stem cell transplantation with Dr. Stuart

Seropian. MedicalMinute There are over 13 million cancer survivors in the United States and over 100,000 here in Connecticut completing treatment for cancers and it is an exciting milestone, but cancer and its treatment can be a life changing experience. Following treatment, cancer survivors can face several long term side effects of cancer including heart problems, osteoporosis, fertility issues and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers to keep cancer survivors well and focused on healthy living. The survivorship clinic at Yale Cancer Center focuses on providing guidance and direction to empower survivors to take steps to maximize their health, quality of life and longevity. This has been a medical minute brought you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven, more information is available at yalecancercenter.org. You are listening to the WNPR, Connecticut's Public Media Source for news and ideas. Gore This is Dr. Steven Gore and our guest tonight is Dr. Stuart Seropian. We are discussing the role of stem cell transplantation for the treatment of cancer. Stuart, before the break you were walking us through this kind of transplantation where people get cells from people other than themselves, donors, that you called an allogeneic transplant, and you were telling us that once these new stem cells were making a new immune system there could be this problem where the new cells were doing some bad to the patient, did I get that right? Seropian Right, and that is graft-versus-host disease, so the graft is how we refer to the donor cells and the 15:49 into mp3 file <http://yalecancercenter.org/podcasts/2014%200427%20YCC%20Answers%20-%20Dr%20Carlson.mp3> host is the patient. This is an illness that can develop if some of the cells in the donor's immune system recognize part of the recipient as different and than cause inflammation. So one of the more common problems that the patient might experience is a rash because the cells from the donor see something in the skin of the recipient that looks different to them and they will attack those tissues because that is the function of the immune system, to protect from foreign proteins or infectious agents or tissue that is different. Other manifestations of graft-versus-host disease include inflammation in the bowel, the GI tract, that can result in symptoms like nausea or loose bowel movements, or the liver, so those are the more common sites that could be affected. Gore That sounds really dangerous if the liver us attacked. Seropian That is actually less common now-a-days and graft-versus-host disease is an illness that can be mild or severe so it is not an illness that if it happens, there is no way to treat it and the transplant will fail. It is something we want to prevent because it contributes quite a bit to the morbidity or potentially mortality of the procedures. I mentioned that this is what makes allogeneic transplant more complicated. Gore So the patient who is undergoing the transplant is probably thinking, I just hope I don't ever get graft-versus-host disease, is that right? It sounds like always a bad thing. Seropian It is kind of a double edged sword and what I mean by that is we are selecting to do this type of transplant when we are hoping the donor's immune system will fight the leukemia or the lymphoma,

whatever the disease is, with standard treatment. Gore How does that work? Seropian We know that the immune system can fight leukemia and that seems most commonly to be observed in patients who get some graft-versus-host disease at some point after the transplant. It is not required and the patients will often tell me they are worried that they know there is potential for the donor's immune system to fight the leukemia and that they have heard that some graft- versus-host disease is a good thing, but they have not gotten it yet and that is not exactly the case, you do not have to get graft-versus-host disease to get an effect from the donor's immune system. We call that graft-versus-leukemia when the donor cells are fighting the leukemia. The first order of business when we do a transplant is to prevent graft-versus-host disease because it really can make patients very sick, but it is one of the reasons why we do not want to keep people on the immunosuppressive drugs that we use to prevent this forever, so we try and stop those drugs when we think a safe period has elapsed where there is no problem that is obvious and then we hope the donor's immune system starts to wake up and starts to do its thing in terms of fighting the disease and we in fact know historically, over many years, that in patients who still have some leukemia 18:56 into mp3 file <http://yalecancercenter.org/podcasts/2014%200427%20YCC%20Answers%20-%20Dr%20Carlson.mp3> after transplant, sometimes when we stop those immunosuppressive drugs, we allow the donor's immune system to sort of wake up and start to work, that patients will go into remission without any chemotherapy and sometimes we will give a boost of cells from the donor, which is usually not very complicated if a patient has a family member as a donor, we just have them come back in and collect some blood and we give that to the patient as a boost to the immune cells which we are looking to fight the leukemia. Gore Wow, I am getting a visual of the old Pacman game with the little guy gobbling up all the enemies, is it something like that? Seropian It is, and this is kind of how we like to think about it, and the correlations with the donor's immune system really fighting the leukemia seem to be best in people who develop what we call chronic graft-versus-host disease and it tends to happen later on often after we stop the immunosuppressive drugs and that is often a milder form of graft-versus-host disease, the stuff that could happen in the first few months, we do not think that is going to help to fight the leukemia, we are just trying to prevent that. Gore Is there any way to pick among a bunch of donors, say which one is going to be the best at getting this graft-versus-leukemia effect? Seropian There are some experimental things, but the first order of business is to have a well-matched donor and we have to choose safety first when it comes to choosing donors. Gore So it sounds to me that this whole thing is pretty complicated and you probably have to be an Olympic athlete or a young person to tolerate all this chemo and then transplant, so what is the upper age limit? 40, 45, and 50? Seropian That is one of the major changes at least since I have been in practice. When I started the upper age limit for transplantation was, in most institutions, around the age of 55 and the reason for that was because probably the hardest thing

to tolerate is the high dose chemotherapy part of the procedure. Now that we have recognized that the very important part of curing cancers is this type of transplant is just related to the immune system helping. There have been methods devised to do transplant without the high dose chemotherapy part. There is always some chemotherapy or radiation that is required, but this can be done with milder treatment that just ensures that the patient accepts the donor graft. So that is referred to typically as reduced intensity transplant or non-myeloablative transplant and because that is a much milder therapy we have been able to extend the age limit up quite a bit. Most institutions do not have a strict age cut off anymore. It is really more of an evaluation of the physical health of the patient. As a practical matter I would say that patients in their early 70s are still considered candidates for transplantation, rarely older than that and usually it is just a matter of patients having other medical problems where it does not 22:10 into mp3 file <http://yalecancercenter.org/podcasts/2014%200427%20YCC%20Answers%20-%20Dr%20Carlson.mp3> seem likely to be safe, but patients routinely in their 60s with diseases like leukemia, myelodysplasia or lymphoma, are considered for transplant and we do not really count people out until we do an evaluation to see how healthy they are and talk about the risks and benefits of the transplant procedure versus the alternatives. Gore That is certainly a big change since 25 years ago when I started in the field, and in those days I would be too old to get a transplant at age 56 for sure, that is really interesting. What happens to the patients who do not have any siblings? I am assuming that if I have a sibling then I have a donor, is that right? Seropian Actually just the way the genetics work, you have a 1 in 4 chance of being matched with one of your siblings. So if you do not have a few siblings you may not have the donor in the family. Gore So 1 out of 4, no matter how many siblings you have? Seropian So if you have a couple of siblings then the chances are increased. It does not double for each sibling. Gore I got it. Seropian You can either be fully matched, half matched, or not matched at all. If the patients do not have a family donor depending on their ethnicity they will be looking at the National Registry, which is linked worldwide now to registries in other countries and there is a good chance of finding a suitable donor through the registry. There are over 9 million volunteer donors who have some form of tissue type in the registry that we can go and look and see if there might be a match there. Beyond that, umbilical cord blood is also a potential alternative donor source as your cord blood is collected at the time babies are born and they are frozen in cord blood banks and you can look for those through the registries or directly through cord blood banks. Gore So they get the blood out of the umbilical cord? Seropian That is right. Gore That is a short little thing. Seropian Yeah, there are not a lot of cells in there, but it is enriched with stem cells and so that has become a very popular source of stem cells for pediatrics because the number of cells needed is in relation to the size of the recipient. So, as you would imagine, you can have a lot more cells per pound of recipient in the pediatric population. It is done in adults as well and that is an alternative, and there

has been work in the last 10 years that looks very promising for choosing family donors who are only partially matched and the special techniques that has been developed to try and make those transplants work. 25:50 into mp3 file <http://yalecancercenter.org/podcasts/2014%200427%20YCC%20Answers%20-%20Dr%20Carlson.mp3> Gore That can't be very safe. Seropian Also the major concern over the years has been that any form of mismatching will result in a higher risk of graft-versus-host disease and that in general is the case. There are ways to give certain chemotherapy drugs to the patients who had a mismatch transplant where we can reduce the risk, so there are lots of different ways to look for a source of these cells in patients when we think an allogeneic transplant is the best treatment for them. Gore What percent of people eventually can find a donor? Seropian Start to finish over half, so unfortunately, particularly if one is an ethnic minority, if there is not a family donor it is harder to find a donor through the registry or through the cord blood, so those patients may be patients where a partially matched transplant would be considered and cord blood would be considered. Gore It sounds like there is still a need to increase the number of donors who are available, is that right? Seropian Yeah, absolutely. Gore Could you tell our listeners that are interested in becoming a donor or being available to be a donor for an unrelated person, how they go about that? Seropian The most direct way would be to go online to marrow.org, the National Marrow Donor website and just follow the links to look for the process for becoming a donor and the donor would receive a kit with just a cotton swab that they run over the surface of the inside of their mouth and this collects enough DNA for the tissue typing to be done. Kind of like the O. J. Simpson case where the DNA was tested that way. So it is very simple, it is not a blood test, it is easy and there is no obligation, if people sign up for the registry they could be called and told that there might be a match and then they would have to go in and give a blood sample and have a medical evaluation, if they might be a donor, but you are not really signing up for anything other than getting listed on the Registry. Gore Does it cost the donor anything to be on the registry? Seropian There is a small fee for the kit, I think it is \$50 or \$60. Gore And does it eventually cost the donor money or does their insurance get charged if they have to be a donor? 27:18 into mp3 file <http://yalecancercenter.org/podcasts/2014%200427%20YCC%20Answers%20-%20Dr%20Carlson.mp3> Seropian No, if one does get selected as a donor there are no costs to the donor, those are covered by the recipient's insurance. Gore And what if my wife was expecting a baby and I wanted to store this umbilical cord blood. First of all, my youngest daughter is getting up there in age now, but we were approached by some places that wanted us to spend a lot of money to put her umbilical cord blood in the freezer for in case she get sick later, so is that what people have to do, pay a lot of money to be on the umbilical cord registry? Seropian There are two different options that we are talking about here, and I certainly have a bias in this regard because I treat patients who have cancer and it is always difficult if you are having trouble finding a donor for the patients who need a

transplant. Cord blood can be collected and frozen with the registry but those are donated to the registry for the use of the general population. So if someone has a baby next month and the cord blood goes to the registry, a couple of days later there could be a request for that cord blood and it could be used for an unrelated individual and I think that right now that is the best use of cord blood. There certainly is a need as we mentioned particularly in ethnic minorities for more grafts for the patients who cannot find donors. There are a lot of companies that will freeze cord blood for individuals for later use either for that baby or for a family member, but a lot of the uses are unknown right now and there is not a lot of regulation and then there is a financial burden. We do not know how long those cells are going to be viable for and we also do not know exactly what the quality control is for the way the cells are frozen and maintained. So, I encourage people to donate to the registry if they are willing, I think it is really a great cause. Gore Do they ask their OB about that, how does that work? Seropian That is the place to start. Dr. Stuart Seropian is Associate Professor of Medicine in Hematology at Yale School of Medicine. We invite you to share your questions and comments. You can send them to canceranswers@yale.edu or you can leave a voice mail message at 888-234-4YCC and as an additional resource archive programs from 2006 through the present are available in both audio and written versions at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another addition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.