Yale CANCER CENTER *answers*

WNPR Connecticut Public Radio

Hosts

Edward Chu MD
Chief of Medical Oncology

Francine Foss MD
Professor of Medical Oncology

Preparing for a Stem Cell Transplant

Guest Expert:
Stuart Seropian, MD

Warren Shlomchik, MD

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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 Ed and Francine welcome Drs. Stuart Seropian and Warren Shlomchik. Dr. Seropian is an Associate Professor of Medical Oncology at Yale Cancer Center and Dr. Shlomchik is an Associate Professor of Internal Medicine and Immunobiology at Yale School of Medicine. Here is Ed Chu.

Chu This evening our topic is stem cell transplantation. Why don't we go ahead and start off by defining for our audience, what is stem cell transplantation?

Seropian I will try to answer that succinctly. Simply, a stem cell transplant is a procedure that we use to treat patients with malignancies, primarily cancers of the blood and immune system. Stem cell transplant is also used to treat patients who have bone marrow failure syndromes. It's a method by which we can support the blood system when we give high doses of chemotherapy or fix diseases where the bone marrow has failed.

Foss Warren, we hear the terms both stem cell transplant and bone marrow transplant. Can you tell us what a stem cell is?

Shlomchik A stem cell was really defined in the hematopoietic system. It is a cell that can give rise to all the other different types of blood cells and it can do that for a long period of time. Stem cells can both regenerate and make new stem cells and also they can differentiate, which means that as they divide they can turn into red blood cells which carry oxygen, white blood cells, which help fight infection, and platelets which help prevent bleeding.

Chu Stuart, what caused the change? I know that when Francine and I were, back in the good old days, in training this was called bone marrow transplantation, so what caused it to evolve from bone marrow transplantation to stem cell transplantation?

Seropian We use the term stem cell transplantation now because we have the option of getting the cells we want out of the bone marrow or out of the peripheral blood or blood system using some special techniques, so when we get the cells out of the bone marrow, which we still do on occasion, that's the bone marrow transplant. When we get the cells out of the blood stream we call that a peripheral blood stem cell transplant, so those are the two main types

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of transplant. I think it's important to back up for a moment to point out that we are not talking about embryonic stem cells for people who are listening, embryonic stem cells are a little more controversial and not really used on a regular basis, these are blood stem cells or cells that are used every day around the world and have been for many, many years.

Chu Now, when one gets these stem cells either from the bone marrow or from the peripheral blood, is there a way to expand the number of cells? Grow them, and then re-infuse them into a particular patient?

Seropian There has been a lot of research in how to expand these stem cells. It's pretty easy and straight forward to expand the cells that are not stem cells, but can only make white cells or can only make platelets, or only make red cells. In the context of peripheral blood stem cell transplantation, this type of expansion is not necessary because we can already get enough cells to quickly allow someone getting a lot of chemotherapy or radiation that knocked down their own blood system, to come back with the donor blood system. It has been more recently studied as a way for cord blood to improve cord blood engraftment. So cord blood, when a women gives birth the blood that is in the placenta has a lot of these stem cells, but there are only enough stem cells to reliably grow in small people, pediatrics, and there has been a lot of research about how to expand cells from cord blood, but none that has really hit the mainstream yet.

Foss Warren, you bring up the stem cells sources from umbilical cord as one of the sources and Stuart, I know that when we do transplantation we look at a number of different donor types. Can you just go through for the audience how we go about picking a donor and what kind of donors we look at?

Shlomchik Sure, I think when people think of the term bone marrow transplant in particular, they think there is a donor involved. Sometimes the donor is actually the patient, so the simplest and most straight forward form of transplantation is to take a patient who has a cancer of the blood or immune system such as lymphoma or multiple myelomas as an example, and in the process of trying to treat that disease more effectively by using more intensive or higher dose chemotherapy, we can collect their stem cells in advance and freeze them and then the patient can receive a very strong, but more effective treatment, and then we just give their own cells back. That's known as an autologous transplant. The times when we think about doing that particular procedure is when the disease in question is very sensitive to stronger dose chemotherapy, so we are trying to cure the patient, we are

trying to provide a more durable remission by intensifying the therapy, and in that case the stem cells make the procedure safe. And because it is the patient's own stem cells, there really isn't a major concern about problems with immune function long term. The second major form of transplantation would be allogeneic transplant, that's where a donor is involved. A family member or unrelated individual is a volunteer, and that's a more complicated procedure, that's really like an organ transplant where we are replacing the blood in the immune system and that's a necessary approach for a patient who has a bone marrow failure syndrome, for instance, severe aplastic anemia. When thinking about doing a transplant and choosing a donor in the family, or an unrelated individual, versus using the patient's own cells, if we have to replace the bone marrow and blood system we are going to choose an unrelated donor or family member. In addition to bone marrow failure syndromes certain cancers do not necessarily respond as well to very strong chemotherapy and we choose allogeneic transplant in those circumstances when we are trying to also get the advantages that giving a new immune system provide us, such as graft-versus-leukemia or graft-versus-lymphoma effect and that's an effect where the donor cells are able to fight the leukemia as well.

Chu Stuart, could you review for our listeners the types of cancers where you think of using say the allogeneic transplant approach?

Seropian The most common would be acute leukemias, so acute myelogenesis leukemia, acute lymphoblastic leukemia. In addition, non-Hodgkin's lymphoma is also common. There are some low-grade lymphomas where we do consider transplantation, although there are many other options for those diseases, but follicular lymphomas for instance, and chronic lymphocytic leukemia, is a very common form of leukemia, but there are some patients who do not do all of the standard therapies that we consider allogeneic transplant for.

Foss Are there also some other diseases such as sickle cell anemia or other diseases that are being transplanted now-a-days?

Seropian That's a great question. Intermittently there has been a lot of enthusiasm for transplanting patients with sickle cell. If you were to look world-wide at any given moment the number of people who would benefit, if it could be done safely, from allogeneic transplant, those with sickle anemia and thalassemia exceed those with leukemia, however, it's a tough decision to make for families because there is always a small risk upfront that someone could die from the treatment and for something that's not an immediately lethal

disease, like sickle cell anemia, it's a very hard decision to make. Although, there have been a number of trials in children who are not doing well, particularly those who have problems with the lung, something called acute chest syndrome or have neurologic problems in their sickle cell disease.

Chu What about the cancers where you would typically think about using an autologous transplant procedure?

Seropian One of the most common cancers that we do autologous transplant for is multiple myeloma, and then aggressive Hodgkin's lymphomas and there are several of those, also a few rare cancers like germ-cell cancers which are often cured with standard therapy, but may recur, are potentially curable with the transplant and then Hodgkin's disease as well may also be cured with autologous transplant, if it recurs after primary chemotherapy.

Foss One of the areas that patients often ask about with autologous transplant is how you are sure that none of my tumor cells are going back in? And there has certainly been some data looking at what we call kind of purging these stem cells products, would you like to talk a little bit about that?

Seropian Sure, it's a good question. When we are performing an autologous transplant we are very careful about selecting patients to make sure that we are doing the procedure in an individual who will benefit from it. If we take a patient who has a lot of multiple myeloma for instance, or Non-Hodgkin's lymphoma where the disease is not well controlled, there really is quite a high risk that we may collect tumor cells and just give them back to the patient, and also our chemotherapy, even in high doses, is not terribly effective. We select patients who are already in a good remission and that decreases the chances of selecting tumor cells. For non-Hodgkin's lymphoma, we have a great drug called rituximab, which I am sure any patient with B cell lymphoma knows already of this medicine and has probably received it and that's the medicine that we give to patients that does purge lymphoma cells out of the blood stream which is where we go to collect the stem cells, so we have good medicine for one disease to do that. For other diseases, there has been a lot of research trying to find and remove tumor cells from grafts. There was a very well designed and conducted study in multiple myeloma that effectively removed tumor cells from the graft and it really did not seem to improve the outcome, so we do know that because there are limits to our ability to get around that problem, if we select the right patients and deliver the right chemotherapy that we still benefit

patients and it's probably the disease the patients have remaining at the time of transplant that contributes to any recurrence of disease, not the contamination of stem cell product with tumor cells.

Chu — I am just curious, is there any age requirement for a patient who is being considered for transplantation?

Seropian — Well, we kind of joke that the age limit is usually the age of the Director of any given program at any given year, and that's just the way of saying that it seems that every decade we have managed to improve the procedure in terms of safety so that older patients are eligible. We transplant patients routinely in their 60s with either type of procedure, allogeneic or autologous, and up around the age of 70 we do become more selective but we don't have a chronologic age cut off. It's really what we call a physiologic age cut off and that's the way of saying that if patients are otherwise healthy, without other major medical problems, and during the pre-transplant testing process we don't discover anything that we think would increase the risk of transplant, we will transplant patients based on the indication of what their disease is doing.

Shlomchik — Some of that stems from the recognition that for an allogeneic transplant some of the efficacy for some of the diseases is really immune mediated, and so these are when the donors immune system recognizes the patient as being foreign and in a way rejects the patient's malignancy, and so for those patients in which we're relying on that effect, you really don't need to give a very intensive chemotherapy or radiation therapy regimen, and so that has allowed a lot of older patients to tolerate that, and as Stuart said, many of us joke that people who pioneered this were kind of the first generation of transplantars who had become too old to get the high intensity conditioning regimens, so we commonly use these types of regimens.

Foss — That will be a great topic for us to jump into during the second part of our program. We are going to take a short break now for a medical minute. Please stay tuned to learn more information about stem cell transplantation with our guests Dr. Stuart Seropian and Dr. Warren Shlomchik.

Medical Minute — *The American Cancer Society estimates that in 2009 there were over 65000 new cases of melanoma in this country. Over 1000 patients are diagnosed annually in Connecticut alone. While melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths, and early detection is the key. When detected early, melanoma is easily treated and highly curable. Clinical trials are currently underway at federally*

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designated comprehensive cancer center such as Yale Cancer Center to test innovative new treatments for melanoma. The Specialized Programs of Research Excellence in Skin Cancer grant at Yale, also known as SPORE grant, will help establish national guidelines on modifying behavior and on prevention as well as the identification of new drug targets. This has been medical minute, brought to you as a public service by Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Radio Network.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss, and we are here today with our guests Dr. Stuart Seropian and Dr. Warren Shlomchik to discuss the topic of stem cell transplantation. Before the break Warren, you were talking a little bit about the whole process of graft-versus-host disease and the kind of conditioning that we do for transplant. Can you back up a step and explain for our listeners exactly what the process is for stem cell transplant?

Shlomchik The first process, as Stuart has mentioned, is having a right patient and so a team needs to evaluate the patient and see if they are an appropriate candidate for stem cell transplant in terms of their disease and their stage of disease. The second process for allogeneic is determining whether they have someone who is what we called a match, and there are certain genes called HLA genes that confer the greatest risk of having immune problems with the transplant, and so we do tests on the patient and then first on their siblings to determine whether they have a family member who is matched at these genes and it's roughly a one in four chance that any given sibling will be a match. If they don't have a match, then we look in registries. People have seen bone marrow drives or ways to register for this registry. It is to see whether there is an unrelated person that also shares these HLA genes. Once that is done, then the actual treatment commences and that comprises of collecting the stem cells from the donor and as Stuart mentioned this is typically done with collecting them from peripheral blood. It turns out that you can give a white cell growth factor that for mysterious reasons causes stem cells to circulate in the blood at high numbers and then there is a machine called an apheresis machine that can collect those stem cells, and then we will give a chemotherapy or chemo radiation regimen to the patient that has a few different purposes. One purpose, especially when it's a higher dose regimen is to try to kill whatever residual cancer cells they have left, and the second purpose of it is to be an immunosuppressant to prevent their own cells from rejecting the non identical donor cells, and then once

that regimen is completed there is some infusion of the donor cells and then the patients are also treated with drugs that suppress the donor immune system to prevent those cells from attacking the patient.

Foss One of the major complications of transplantation is the rejection process, the process called graft-versus-host disease, and I know Warren, you have done a lot of research in that area. Can you let our audience know a little bit about what that process is and what we can do about it?

Shlomchik Well most people don't have autoimmunity and that is you have immune cells in particular, T-lymphocytes that help fight infection and they go around and they can recognize lots of different proteins, but they don't attack you because as they developed those cells that could potentially attack you are either killed off or rendered non-functional. However, even in a sibling they differ in many, many proteins and that's why unless you have an identical sibling, you look different than your siblings and all of those things that help make you look different those things can cause differences in proteins, and those can be recognized by the donor cells as non-self and so when you infuse those cells in, those cells go around and they treat you as if you have a viral infection in every cell, and they can get activated and those that are reactive against the donor can actually go and attack some of the tissues of the patient and the tissues that are classically involved are the skin, the liver, and the gastrointestinal tract.

Chu Then the patient would present with what, a skin rash, or diarrhea, dysfunction of the liver?

Shlomchik We carefully examine the patients after the transplant, and we look to see whether they develop skin rash, or they can develop a diarrhea, as you said, and then we measure in the blood things their liver makes or can be released from the liver and those would give us indications that there could be an immune response against the liver.

Foss Stuart, you have done a lot of work and you have a protocol now looking at drugs that might help prevent this rejection.

Seropian I should mention that unless we are doing a transplant from an identical twin we always have to provide some method to prevent graft-versus-host disease. We do not just give the cells from the donor and wait and see what happens. The most commonly used way we to try and prevent graft-versus-host disease is to use immunosuppressant medicines that typically target the cells that Warren was mentioning, lymphocytes, and prevent them from being over active and that's effective in many people and we always try to

find ways to make those drugs more effective. Graft-versus-host disease is particularly problematic when we don't have a well-matched donor and there are situations in leukemia in particular where we know that a transplant from a mismatched donor, although suboptimal, may still be the best option to try and cure an otherwise incurable disease. We have been studying new drug combinations at Yale for several years and think that things are working better and this is really the focus of most research in allogeneic transplant, trying to find new ways to prevent this problem of graft-versus-host disease.

Chu I am just curious, about what fraction of patients who undergo allogeneic transplant will develop graft-versus-host disease? Usually what's the time frame from the point that someone undergoes the transplant to developing graft-versus-host disease?

Seropian I think a good number to remember is a big picture number, it is probably about half, so it's very common. I think the important thing is that what we are trying to do is prevent severe graft-versus-host disease. We have known for a long time that there is an association with graft-versus-host disease and patients not relapsing, so we kind of think of graft-versus-host disease as a double-edged sword so to speak. What we do not want is a severe form that makes patients very ill and also requires a lot more immunosuppressant medications that open the door for infections.

Shlomchik That's a good jumping off point to talk about why we subject people to the risk of graft-versus-host disease which Stuart is mentioning, and it is really this immune effect against particularly the leukemia's and lymphomas. It's worth pointing out that you may read in the newspaper about cancer vaccines and immunotherapy for cancer, but this as a field was really invented in the bone marrow transplant field and I think more people probably get cured every month in the world by the immune effect from bone marrow transplant then in the entire history of immunotherapy for other cancers. For example, probably the best example, was chronic myelogenous leukemia in which if you relapsed after your transplant, you could just get white cells from your original donor and go into complete remission and the effect is so strong that even if they use the most sensitive methods using DNA to detect the leukemic cells, you cannot find them.

Foss Warren, basically you are saying that if you have a stem cell transplant in the case of CML, for instance, your disease comes back and certainly this is true in lymphomas as well, that you can go back and just get peripheral blood cells for the patient from the donor?

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Shlomchik Exactly right, I mean for CML we don't do very many transplants anymore because of Gleevec and other drugs that are very effective, but we still see, particularly as you mentioned for low-grade lymphomas and chronic lymphocytic leukemia, the immune effect is very strong and in fact you can follow in the blood using sensitive methods over time someone who has had transplant for CLL and you can watch the amount of CLL that they have in cells go down over time, even though they haven't had any chemotherapy for months, and so it's very potent. I think there are two principle challenges, one is how do you get this immune effect without having toxicity of graft-versus-host disease and the second is how can you make cancers that are not as susceptible for reasons that we do not understand to be more susceptible?

Foss And Warren, you have a very innovative clinical trial that is just getting started at Yale Cancer Center. Can you talk a little bit about that trial?

Shlomchik Sure, in the lab we found that a certain type of T cell called the memory T cell, these are T cells that have previously responded say to an infection and then live in you for a long time in order to protect you from future infections, have a reduced capacity to induce graft-versus-host disease, and one of the main problems of doing an allogeneic stem cell transplantation is actually immune reconstitution. Patients are very susceptible to getting infections, and there are many centers that feel that toxicity from the graft-versus-host disease is so high that for patients who can get high intensity chemotherapy regimens or radiation regimens, they actually will physically remove the T cells from the donor graft figuring that, although there is an increased risk of relapse, there is a decreased risk of having toxicity from the graft-versus-host disease. However, a major problem with that is that because no T cells are given there is poor reconstitution of memory against infection, so what our protocol is, is to give patients who have acute leukemia who are young enough and healthy enough to have a chemotherapy regimen that will be very active against their leukemia to selectively give them memory T cells and in that way we would reconstitute their T cell memory. We also know from the lab that these cells have some ability to mediate the so called graft-versus-leukemia effect, although we do not really know in humans whether it is stronger or weaker. Our longer term approach to this is actually to vaccinate the donors against proteins that are on leukemia, make memory cells and that way when we transfer memory cells we will both improve the patient's ability to fight infection and also improve the graft-versus-leukemia effect, and I should say that in mice that approach works spectacularly well and we will see how it works in humans.

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Chu Stuart, other than graft-versus-host disease, are there any other side effects or complications that are associated with transplantation?

Seropian Sure, and that depends a great deal on the therapy that was chosen for an individual patient. When we are doing a standard transplant in a younger individual and giving a very high dose of chemotherapy, there are side effects with that treatment and that includes discomfort in the form of mucositis, which is injury to the lining of the mouth, or throat, or the bowels. There is a risk of infection and the blood counts do get very low, although temporarily, and so patients need transfusions and there are other organs that may be susceptible to the effects of chemotherapy. Pre-transplant testing is really designed to make sure that we are not giving too strong a treatment to an individual who cannot withstand it. Fatigue is a very common symptom following transplant, and common after a lot of different types of anticancer therapy, but that is particularly common as well.

Foss Stuart, taking care of these patients in the hospital is a real challenge because of the multiple issues, can you talk a little bit about the multidisciplinary approach for managing these patients at Yale Cancer Center?

Seropian We collaborate with physicians and a lot of different specialties both before and after transplantation. Some of the disciplines that come to mind right away are the infectious disease doctors who help us in terms of making sure that there are no infectious problems before transplant that might come back. In a situation where we are compromising the patient's immune system temporarily, the pulmonary doctors help us quite a bit, and the nephrologists, or kidneys doctors, are also really crucial to our practice since many of the medicines that we use effect the kidneys.

Shlomchik I would also add to that radiology. We do a lot of imaging in our patients and having radiologists that are experienced in the types of issues of bone marrow transplantation, is really important.

Chu Great, and in the remaining few seconds that we have, if there are listeners out there who would like to learn more information about transplantation and the folks involved, is there a phone number or website that you can provide to our listeners?

Seropian Probably the best portal of entry is the Yale Cancer Center website at yalecancercenter.org and the Hematologic Malignancies Clinic is at 203-200-HEME, so those are two other places to go for more information.

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Chu Terrific, well Warren and Stuart, thank you so much for being with us this evening on Yale Cancer Center Answers to discuss stem cell transplantation. We certainly look forward to having you back on a future show to discuss all the great progress that has been made in the world of transplantation. Until next week, this is Dr. Ed Chu from Yale Cancer Center wishing you a safe and healthy week.

If you have questions or would like to share your comments, visit yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.