

Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and he is an internationally recognized expert on colorectal cancer. Dr. Foss is a Professor of Medical Oncology and Dermatology and she is an expert in the treatment of lymphomas. If you would like to join the discussion, 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 Dr. Stuart Seropian. Dr. Seropian is an Associate Professor of Medical Oncology at Yale Cancer Center and an expert in stem cell transplantation for cancer treatment.

Chu Stuart, before we go into discussing bone marrow stem cell transplantation, can you set the stage and explain how you got interested in this field of stem cell bone marrow transplantation?

Seropian When I was training I gravitated towards what we called the liquid cancers, or hematological malignancies, so diseases like non-Hodgkin's lymphoma, multiple myeloma, and leukemia. Those are diseases that respond very well to chemotherapy, standard treatments do very well for those patients, but transplant was a very interesting type of therapy with a lot of science behind it and showed great promise in terms of curing a significant fraction of patient's. I could see that this was a field that was changing and evolving rapidly and I wanted to be a part of that area of clinical care and research.

Foss Stuart, for our listeners, could you clarify again what is a stem cell?

Seropian Sure, I think that this is an important point that can be confusing to the general public. There is a lot of controversy about research in embryonic stem cells, but that is not what we are talking about in the clinic for the care of our patients who have cancer quite yet. Stem cell transplant is simply put, the transfer of cells that are capable of differentiating, or growing up, if you will, in deformed blood cells. These are more grown up or mature blood cells, they are not embryonic stem cells, and there is very little controversy in terms of their use in clinical care.

Foss I understand that these stem cells can come from either the blood or the bone marrow. Can you tell us a little bit about the differences? We used to call this bone marrow transplant and now we are calling it stem cell transplant, can you clarify that for us?

Seropian Stem cell transplant is a very generic term. If we go back 20 years or 30 years, what we had was bone marrow transplant, it was getting these cells out of the bone marrow. In the 1990s, we found that we could get similar groups of blood cells out of the blood stream using special techniques, and that's what we call a blood stem cell transplant. We use the generic

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term stem cell transplant nowadays to talk about these procedures, but they are not all the same. When we get cells out of the peripheral blood, we are able to harvest and then subsequently transfuse higher numbers of the cells that are important for patients to recover the blood counts in the early period after transplant, and for many patients that has some major advantages.

Chu There are different types of stem cell transplants, can you talk about that a little bit?

Seropian Sure, there are two major types of stem cell transplant, autologous stem cell transplant and allogeneic stem cell transplant. With the autologous type, we are harvesting or collecting the stem cells from a patient's blood stream, freezing them, and then we use them at a later date. That type of transplant is used to try and give patients stronger chemotherapy and we support that therapy with their own cells. An allogeneic transplant is really a different type of procedure where we are getting the cells from a donor. It might be somebody in the family, or it might be an unrelated donor, and in that case, unless the patient has an identical twin, which is uncommon, we are giving a patient a new immune system. We can use those cells to support the administration of a high dose of chemotherapy. In a similar fashion, in the case when we are using the patients own cells, we don't always do that, sometimes we want to give the patient a new immune system to try and get the advantages of that new immune system in terms of fighting cancer.

Foss What kinds of cancers are typically treated with a stem cell transplant?

Seropian Well, I mentioned that I got into this because I was interested in the liquid tumors, or diseases of the blood, marrow, and immune system. Those are diseases like multiple myeloma, the acute and chronic leukemia's, non-Hodgkin's lymphoma, and Hodgkin's lymphoma. What those diseases have in common is that they tend to respond very well to standard doses of chemotherapy, and transplant, in many cases, involves giving higher doses of chemotherapy that are even more effective. There are some other diseases that we also consider for transplantation such as a germ cell tumor, testicular cancer for instance, is not a traditional cancer of the blood, marrow, or immune system, but is also a disease that responds well to chemotherapy, and in certain cases, a transplant will help to cure people. The last category is bone marrow failure syndromes. Those are not cancers, but diseases like aplastic anemia where patient's marrow is not functioning and may in fact be gone, then transplant is more of a replacement therapy, but the same techniques are applied.

Chu As you are mentioning these different diseases, they are all what we would call potentially curable diseases. So in what setting would you decide to use a transplantation regimen as opposed to standardized care, traditional chemotherapy?

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Seropian I should say that not every transplant is performed with the intent of trying to cure patients. There are certainly situations, in particular when we are using the patients own cells and there aren't the potential complications involved in trying to give the patient a new immune system, where we are really just trying to give more effective therapy and keep people in remission for a longer period of time. Multiple myeloma I think is the primary example of that where a high-dose chemotherapy in their own cells is very safe, it's often an outpatient procedure, and we don't think it makes the myeloma go away, but we gain anywhere between a year and a half to three years on average of extra remission time. That's particularly important in this day and age where a lot of new therapies that are coming along may be available for a patient in another year or two and transplant can propel patients forward so that they can take advantage of those therapies. The decision of what type of transplant to perform and when, is a complex decision, it depends on the patient's age and their medical condition. It is a general rule that we offer transplant to patients when we think standard therapy may not work well enough for them or may not cure them, but they are responding to it. Transplant in general is not a good therapy for people who are not responding well to the treatment they are receiving.

Foss Stuart, we talk a lot about transplant in the clinic and often times it's a scary word for patients because they have read some old statistics about patients dying from these kinds of procedures, but the whole world of transplant has really changed in the last couple of years and I wonder if you could touch on that for our listeners, in terms of what ages we can transplant patients and what new medications have developed to deal with the complications of transplant?

Seropian I sometimes joke that I am a little spoiled because transplant is an awful lot different nowadays then it was even 15 or 20 years ago when I was just starting my training. When we use a patient's own stem cells, and we are not replacing their immune system, they get a course of high-dose chemotherapy. This is generally applied to patients who responded to their initial therapy and the risk of a major complication, the risk of mortality, is really quite low. As I mentioned, we do these procedures as outpatient procedures, and at Yale our one-year treatment related mortality is less than 1% and that's a very similar statistic to what you will hear from major transplant centers around the country. When we replace the patient's immune system with an allogeneic transplant, the numbers are much more variable. There is a higher risk of certain complications, which I will talk about, and that being said, some of the advances in the last 15 years have really changed the candidacy of transplant for patients in that we are transplanting older patients because we can use peripheral blood stem cells for instance, and the patients get better more quickly. So, allogeneic transplant, which is generally considered the more complicated procedure, we can in fact perform in patients up

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until the age of 70, early 70s, and we have performed procedures for patients in that age group, it is actually quite common for either type of transplant, to be offering this therapy for patients in their 60s. I would say it depends a lot more on the patient's medical condition, their disease, and other factors than their mere chronologic age.

Chu As you say, with one of the transplants you give back either the patients bone marrow or peripheral blood, is there ever any concern that there might be cancer cells contaminating that sample when you re-infuse it with their own cancer cells?

Seropian Sure, when we are doing an autologous transplant using patient's own cells, we do have that concern. That's one of the reasons why we don't have much enthusiasm for trying to perform that procedure if the patient is not responding well to the initial therapy. As an example, if a patient has multiple myeloma and they have a very good response to their initial treatment, there are not likely to be many tumor cells in the blood for us to be re-infusing. That is why if a patient has an identical twin where the immune systems are exactly the same genetically, we prefer to use the identical twin as the donor. There has been a lot of research trying to figure out what the contribution is of re-infused tumor cells in these types of therapies and most of that research suggests that if you are performing the procedure in appropriate patients that's really not a major problem.

Foss There has also been research looking at ways to purge those tumor cells out of the autologous stem cell product and that hasn't really made a big difference in my understanding, could you talk a little bit about that?

Seropian In a lot of the older laboratory techniques, that's correct. It was hard to do that without damaging the normal cells in the graft. In multiple myeloma, there was a technique to that that didn't result in a major improvement, despite the fact that the tumor cells could be removed from the graft. Nowadays, we have this great drug for non-Hodgkin's lymphoma called Rituxan, which you are very familiar with, and this therapy actually does a very good job of getting the lymphoma cells for those patients out of the blood stream so that when we collect the stem cells, we have what we call in vivo purge that means getting rid of the tumor cells out of the blood stream in the patient before there stem cells are collected. It is not applicable to every disease, but a lot of the transplants we perform are for non-Hodgkin's lymphoma.

Chu Do you do any kind of testing to see whether or not there are some tumor cells floating around in that autologous transplant?

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Seropian We can test the blood and the blood product when cells are collected. We don't always do that, it's not clear how important that is, it's more of a patient-by-patient situation.

Foss Stuart, can you touch on the role of radiation as part of the autologous transplant or the allogeneic transplant procedure? I know we used to do a lot of radiation and we are not doing it as much any more.

Seropian That's correct. I think it plays a more major role still in allogeneic transplant. This is something that is somewhat dependent on the preferences of the treating institutions and autologous transplant for diseases like lymphoma and myeloma, which are the major indications that radiation doesn't appear to add very much. We prefer to use chemotherapy as do most centers do. It's an important modality for allogeneic transplant because it helps to prevent donor cells from being rejected, but it's not that only way to do that and in fact there is a lot of interest in applying lower doses of radiation and getting the same benefit.

Foss I would like to talk in more detail about the specific types of transplant when we come back from the break. You are listening to Yale Cancer Center Answers and we are here with Dr. Stuart Seropian discussing cancer treatment with stem cell transplantation.

*Medical
Minute*

Over 170,000 American's will be diagnosed with lung cancer this year and more than 85% of these diagnoses are related to smoking. The important thing to understand is that quitting, even after decades of use, can significantly reduce the risk of developing lung cancer. Now, everyday patients with lung cancer are surviving thanks to increased access to advance therapies and specialized care and new treatment options are giving lung cancer survivors new hope. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for lung cancer and patients enrolled in these trails are given access to medicines not yet approved by the Food and Drug Administration. This has been a medical minute and you will find more information at [yalecancercenter.org](http://www.yalecancercenter.org). You are listening to the WNPR Health Forum from Connecticut Public Radio.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by my co-host Dr. Ed Chu and Dr. Stuart Seropian, Associate Professor of Medical Oncology at Yale Cancer Center. Stuart, before the break we were talking in detail about the use of radiation for transplant. I would like to take a step back now and have you review for us the process of a patient undergoing an autologous transplant or an allogeneic transplant. Could you just take us through what that looks like from a patient's point of view?

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Seropian Most patients who have the diseases we are talking about are cared for by a hematologist or oncologist around the state and then come to the transplant center for consideration of transplant. Sometimes it's clear that an autologous transplant or an allogeneic transplant might be indicated, but that's always part of the initial evaluation, to think about which type of procedure would work best, if we think transplant would be appropriate. The process is very different for the two different types of transplant. For an autologous transplant, there are two steps for the procedure in a general way. The first step is to collect and freeze, or cryopreserve, the patients own stem cells. We have to do that prior to giving a course of high-dose chemotherapy, after which the stem cells are thawed out and re-infused; just like a blood transfusion. There are several days of stem cell collection where the patient comes down to the center to have it performed as an outpatient procedure. They get a little bit of a break and then they undergo the high-dose chemotherapy and receive their stem cells. After they have received their stem cells, and they have had the high-dose chemotherapy immediately prior to that, they observed in a similar fashion in many ways to when they have had previous chemotherapy in the past, but the treatment is stronger, so the observation period is more intensive in terms of time, antibiotics, and other supportive care measures. It is quite common for patients to require hospitalization, although it's not mandatory. In a very general way we describe to patients that an autologous transplant includes a step where we have to collect the stem cells, but that it's similar for most patients to therapy they have had before in terms of chemotherapy, only stronger, and requires more time at the transplant center.

In allogeneic transplant, the process is quite different because we have to identify a donor. When patients come to see us we have a longer conversation about some of the potential complications of that procedure; it does require a month long hospitalization. The donor collection is a separate issue that the patient doesn't typically participate in directly. If there is a family donor sometimes they are there for some of those procedures, but the family donor comes in as a separate medical evaluation and the collection of the stem cells for the family donor is done, at our institution, ahead of time and we freeze the cells. In some institutions it takes place simultaneously with the transplant. If there is no family donor, then we have to look in the national registry to see if we can find a donor who is compatible, and there is special testing that needs to be done, genetic testing, to look at the genes in the immune system to match them up with the patient. If we are lucky, that will only take four to six weeks, but it's much more common for that to take 12 weeks, or sometimes longer. We will see a patient and we may think an allogeneic transplant is the appropriate procedure for them, and we will initiate a search and then the patient will need to continue on appropriate therapy. They may come back to the center several times to monitor how they are doing in terms of their illness and at the same time update them on how things are going with the search and talk on several more occasions about the nature of an allogeneic transplant in terms of the hospitalization. But more importantly we talk about what happens after the

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transplant when they go home, they have a new immune system. They have to take medications to make sure the new immune system functions properly and doesn't cause complications, they have to take a lot of antibiotics, and that period of time after an allogeneic transplant, in contrast to an autologous transplant, can be quite lengthy; a minimum of six months with fairly intensive followup and medications, but much more commonly a period of a few years taking care of the new immune system.

Foss Can you talk a little bit about this process of donor matching for patients that don't have a family donor? How do we go about identifying donors and how often do we actually find a donor for patients that need a transplant?

Seropian For patients who don't have a family donor, we can get a rough idea of the chances of finding a donor in the national registry fairly quickly. The patient has to have a test called HLA typing and then we input the HLA typing into the database of the National Marrow Donor Program and get a print out of potential donors for that patient. I would emphasize the term potential, because although there are almost 7 million donors that we have access to in terms of their typing, a lot of it is not complete. Donors may have been typed for one reason or another, sometime in the last few years or much longer ago, and so we can see donors that may be match the type of the patient, but then we have to have further testing performed by the National Registry in the same lab where the patients testing was done to confirm that. That can be quite a lengthy process. The chance of finding a donor really depends on the patients HLA type, their ethnicity. I think we have gotten better in the last ten years, primarily because of the fairly major increase in the number of donors in the registry.

Chu Stuart, can anyone who lives in United States be a potential donor, be part of the registry, or are there certain criteria that are required to be a donor?

Seropian If they are between the ages of 18 and 60 they can, and it's not difficult. In fact, go to the National Marrow Donor website, marrow.org, and there are fairly simple instructions to get typed, and this can be done basically via the mail. Kits can be sent and just as a swab in the mouth and the genes are there to examine.

Foss We have seen a lot of examples of programs where patients can't find a donor and then there is a solicitation in a community for people to come forward to potentially become donors. How often, in a situation like that, do you actually find a donor for that particular patient? Or is that more of a way of getting people involved?

Seropian I think it's probably the latter. If we are searching the registry of almost 7 million donors and we don't find a match, then a donor drive that adds another 100 or 200 donors statistically

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may not find us a donor, but those donor drives are how the registry got so large to begin with and that's why we are having better success finding donors for all our patients. We always encourage donors and families to pursue donor drives and encourage more people to get on the registry.

Chu If there is a situation where you know do this exhaustive search and you can't find a match donor, will you go ahead and proceed with the transplant if in fact the patient really needs to have the high-dose chemotherapy in the transplant?

Seropian I had mentioned exactly what the criteria are and we are always looking for fully matched donors, as we think the outcome is best. We know now, based on advances in the laboratory in terms of typing patients and donors that, particularly in the 1980s, but even in the 1990s, a lot of the unrelated transplants that we thought would match well did not match very well. A lot of information was gathered regarding what we can perform in terms of donors who aren't fully matched. Whether we will transplant patients who aren't fully matched depends on where the mismatches are, and in particular, how many of them. We have better drugs nowadays to prevent some of the complications that can occur when the donor and patient aren't a match. We do have more enthusiasm for that procedure, but that's a complex decision that depends on the patient's condition, it depends on their illness, and it depends on the nature of mismatching, but we are doing mismatch transplants and many centers are.

Foss I understand that you have a protocol here at Yale for managing the complications of mismatch transplantation, can you tell us a little bit about that?

Seropian Well, we got interested in this years ago when some newer drugs became available, specifically to try and reduce the frequency of an illness called graft-versus-host disease, which is a reaction that can occur when the donors immune system recognizes some tissue in the patients as being different and causes symptoms such as a rash, or inflammation of the liver or the bowels, and that's the major potential complication of an allogeneic transplant. We found several years ago that using some of the newer drugs available to prevent these complications in our standard transplants were working better and we applied them to patients who had mismatch donors and found the same thing until we formalized a protocol, in fact we presented some of our preliminary results in one of the national meetings last year because we think this is a significant advancement as to certain patients that we might have been reluctant to perform transplant years ago and now we will take a mismatch donor and perform that with some of these newer drugs to prevent that complication and it seems to be working out pretty well so far. We have done well because we are not an overly large center, we are sort of medium-sized center, but a very dedicated team of professionals, I would emphasize that this is really sort of group effort, we have search coordinators who are able to

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find donors and we have a very experienced core group of nurses in our bone marrow transplant unit that have been taking care of patients for many years, and a day hospital, or outpatient facility where the continuity is very good. We certainly have taken advantage of a lot of the new things that have come along in transplant, like these new drugs that I think are resulting in better outcomes for our patients. We do about 120 to 140 transplants a year; more autologous than the allogeneic type. We have a pretty busy program and patients have a choice, they can come to the center of the state, or they have to go to one of the major cities on the east coast, New York or Boston otherwise.

Chu It's amazing that time has gone so quickly, and hopefully we will have you come back and we can hear about some of the research, the very active research, that is going on in your transplantation program. You have been listening to Yale Cancer Center Answers and I would like to thank our guest, Dr. Stuart Seropian, for joining us this evening. Until next week, I am Ed Chu from Yale Cancer Center wishing you a safe and healthy week.

If you have questions or would like to share your comments, go to 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 from Connecticut Public Radio.