

Support comes from AstraZeneca, working to change how cancer is treated with personalized medicine. Learn more at astrazeneca-us.com 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 stem cell transplants with Dr. Stuart Seropian. Dr. Seropian is an Associate Professor of Hematology at Yale School of Medicine. Dr. Gore is a Professor of Internal Medicine and Hematology at Yale and Director of Hematologic Malignancies at Smilow Cancer Hospital. Gore Stuart, I think a lot of people have heard a lot about stem cell research and all the controversies around stem cell research and embryos. And when they hear about stem cell transplant, is that the same thing? Seropian They are very different things, Steve. Stem cell transplant is used to treat cancers, predominantly cancers of the blood and some other cancers, but the stem cells that we use are not the embryonic stem cells we hear about in the news where there is controversy. These are cells that make blood and other elements of the immune system and they are used to a clinical purpose. They have been around for more than 30 years and there is very little controversy about their use. Gore That sounds a lot like what I thought was called bone marrow transplant. Seropian With stem cell transplant, in fact, they did start with bone marrow as the source for the cells and that is still used today, although stem cells can also be procured from the blood and more stem cell transplants are performed with cells that are procured from blood nowadays than bone marrow. So, bone marrow transplant is a form of a stem cell transplant. Gore Can you walk our listeners through what is involved in a stem cell transplant, who might get one, and what might happen if they have one? Seropian Patients are referred for stem cell transplants usually by a treating hematologist or oncologist who is managing a case of blood cancer, typically, so that would be a disease like multiple myeloma for instance. That is the most common indication for a transplantation around the world. But other diseases like leukemia, lymphoma, myelodysplasia, also some diseases of the bone marrow that are not cancers such as aplastic anemia for instance. Patients may be referred for consideration of a transplant. There are two major different types of transplantation that are different with regards to the manner in which they are conducted, but also different in terms of the mechanisms by which they may help a patient. 3:09 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0304-Podcast-Seropian_328701_5_v1.mp3 An autologous stem cell transplant which is the most common procedure involves using the patient's stem cells which are taken from the blood and frozen and they are administered later on after a patient receives very strong chemotherapy. Gore So, these are the patient's own stem cells? Seropian That's correct. And their purpose is to help rebuild the blood system after very strong chemotherapy is administered so that strong chemotherapy can be administered safely. So, the mechanism by which that transplant may benefit a patient is really by allowing us to give a very strong treatment, a very strong chemotherapy regimen. The

other major type of transplant is referred to as an allogeneic transplant. Gore Allogeneic? Seropian That's correct. In that case, the cells are obtained from someone else. So, typically a patient with leukemia may need a transplant and we do not want to use their cells. Gore Why not? Seropian Leukemia grows in the blood and the bone marrow and often if you try to collect stem cells from the blood or bone in those patients, you will collect many leukemic cells, so that can be problematic. The use of very strong chemotherapy is a component of treatment that may help leukemic patients, but it often does not cure those patients. When we get cells from a donor such as a sibling, a brother or a sister or an unrelated donor, we are replacing the immune system and it is often the action of the immune system that helps to cure the patient. Gore Could you explain that more? Seropian Many people probably hear the word immune system in the news nowadays as a very powerful tool to fight cancer, there are a lot of different forms of immunotherapy that are being developed or have been developed that are being used now for patients. Gore I have seen some of those on commercials on TV. Seropian And they are useful for many cancers. The allogeneic transplant, one might think is one of the original forms of immunotherapy. When we replace a patient's blood and immune system with the stem cells from a donor who is a match, typically a brother or sister, we are replacing the immune system with an immune system that always has some differences unless it is an identical twin where matching patients with their donors as best we can with 5:42 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0304-Podcast-Seropian_328701_5_v1.mp3 the genes we know are very important in the immune system, but there are always some differences between the immune systems of siblings or patients and volunteer donors. These differences turn out to translate into some action of the donor's immune system, identifying cancer cells in the recipient or patient and that results in improved cure rate compared to a lot of other therapies. Gore What you are saying, as I understand it, is that the donor cells, although they are matched, somehow are fighting residual cancer cells? Seropian That's right. In fact, there is a term for that in the transplant literature that is called graft-versus-leukemia, the graft of the donor cells, and they react against the leukemic cells. The allogeneic transplantation really is an organ transplant where we are replacing a part of the body just like a patient who needs a new kidney gets a kidney transplant. In this case, there is no surgery, it is blood therapy, but it is an organ transplant where the patient gets a new immune system. Because it is always a little bit different, there can be reactions against other normal tissues. So, it is a more complicated procedure, but that graft-versus-leukemia effect seems to be pretty powerful and results in high cure rates for leukemias compared to a lot of our other therapies. Gore You said there is no surgery, so how do they get the bone marrow into the bone? They do not have to put some kind of needle in the bone and inject it do they? Seropian If the donor cells come from the bone marrow or from the peripheral blood, they are still a blood product that may look indistinguishable from a regular bag of blood and it is infused in the blood stream and the stem cells are programmed to

go back to the bone marrow, which is where they will set up shop and start making blood that usually takes a few weeks, and during that time, patients are typically in the hospital, although not always, and they do require special support. Gore That sounds great if you have these commando cells going after these cancer cells. Why wouldn't all these patients who need transplants like those myeloma patients who we are talking about and stuff, why don't they get donor transplants typically? Seropian Some do and it is not always clear which type of transplant is best for any particular patient. When we think a patient can benefit by a transplant using their own cells with the use of strong chemotherapy, we prefer that procedure because it is much safer, it is simpler, recovery time tends to be shorter, and in the case of myeloma for instance, there are many good therapies for multiple myeloma that are available nowadays – transplantation is one of them and it can help many patients, but many patients can do very well for a very long period of time either without transplant or with the incorporation of transplant and continuation of other therapies. That is a disease where an autologous transplant, using the 9:04 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0304-Podcast-Seropian_328701_5_v1.mp3 patient's own cells, has fit in very nicely and is associated with fairly long survival times. Other diseases like acute leukemia, that graft-versus-leukemia effect is necessary for many of those patients if they are going to survive long term. So, it is a riskier procedure because of the immune complication or the potential for those immune complications. But we tend to choose that procedure when we feel like the other therapies we have are not going to benefit the patient on the longer term. Gore So, what I am hearing is it kind of depends on the biology of the disease I guess? Seropian That's correct. There are other factors, the health of the patient, the availability of a well-matched donor, and the state of the cancer in question. Gore How easy is it for patients to find a donor, I mean I have got 2 siblings and if God forbid I need one, I guess I would ask them to do it right? Seropian You have a 25% chance of being fully matched with one of your siblings. Nowadays, we are fairly successful in finding donors for most of our patients because we have many donor options. We prefer a sibling and that is the most tried and true straightforward way to perform a transplant with a donor, but there is a worldwide registry now of volunteer donors who have preliminary testing that we can access very quickly to see if we might be able to find an unrelated donor through the National Marrow Donor Program or from other parts of the world that are connected to the National Marrow Donor Program. And then, there are other ways to do transplant with donors who are not fully matched. Gore We probably want to talk about that in a few minutes because that certainly sounds very interesting, but let us go back to kind of these more typical situations, so if a sibling were to be available to donate some blood, is that how it works? Seropian The testing to determine the compatibility with the donor and recipient can be done with blood tests or for donors who are not local, we send them a little kit that has what looks like a Q-tip and they get some DNA from their cheek, they just swab the inside of their mouth and they mail it in and we test the genes. There are 10 genes

that are usually tested and we want to match those up. That takes a week or two. If the donor is identified and matched, they come to the center and have a medical evaluation and typically will receive an injection for 4 days of a medicine that will get the stem cells out of the bone marrow into the blood in high numbers, and these cells can be collected from the blood stream through a procedure called apheresis. Gore That sounds complicated. 12:22 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0304-Podcast-Seropian_328701_5_v1.mp3 Seropian It is a little bit like donating blood, and it takes several hours and it might be done for one day or two days really, three days and well it is an outpatient procedure and it is fairly well tolerated, a little tiring, people usually take a few days off from work afterwards. Gore But no major long-term effects for the donor? Seropian Generally, no, a very safe procedure and of course, donors are qualified to make sure that they are healthy and there are not any additional risks or concerns. Gore How do you organize? Say a donor is in Russia or India or some other place, do they have to come here and do that? Seropian If it is a sibling donor, then we do try to get donors to come to our center, although the National Marrow Donor Program has a new program that is available to some donors around the world where a sibling can go to a donor center that works with the National Marrow Donor Program and have their cells collected in the same fashion as a matched volunteer unrelated donor would do. Gore And then the cells are shipped? Seropian Yes. The cells are shipped. They are put in a cooler and then they are brought here by a courier, it is not FedEx. Gore And that is the same as true with the voluntary donor? Seropian That's correct. And that is done in real time, meaning when a transplant is planned, a patient is admitted to the hospital and they receive chemotherapy and a day or two before the transplant, the donor cells are collected and they are brought via courier to our center and then they are administered to the patient on the day of the transplant fresh within 48 to 72 hours. Gore It's a lot of planning, it sounds like. Seropian Lots of moving parts. Gore A lot of moving parts, that you have to coordinate well. This is really a very interesting subject and I am certainly going to want to hear about these alternative kinds of transplants that you mentioned, but right now, we are going to take a short break for a medical minute. Please stay tuned to learn more information about stem cell transplantation with Dr. Stuart Seropian. 14:36 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0304-Podcast-Seropian_328701_5_v1.mp3 Medical Minute Support comes from AstraZeneca, a biopharmaceutical business that is pushing the boundaries of science to deliver new cancer medicines. More information at astrazeneca-us.com. This is a medical minute about breast cancer, the most common cancer in women. In Connecticut alone, approximately 3000 women will be diagnosed with breast cancer this year, but thanks to earlier detection, noninvasive treatments and novel therapies, there are more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer. Digital breast tomosynthesis or 3D mammography is transforming

breast screening by significantly reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety many women experience. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio. Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore, and I am joined tonight by my guest, Dr. Stuart Seropian. We are talking about stem cell transplants for the treatment mostly of blood and bone marrow cancers. Stuart, you had mentioned before the break that there are now more sources of stem cell donation or donors besides traditional siblings and voluntary match donors. First of all, how many patients in general find a donor with those first two searches – the siblings and the donor registries? Seropian It depends in part on our ethnicity actually, and of course the number of siblings you have. But we find matched donors in the family less than half the time, so we often turn to the registries, the worldwide registries, but not all ethnicities are equally represented in the registries, so we may find a matched donor in more than half of Caucasian patients who are of European descent. But the statistics are much lower for other ethnicities, sometimes as low as 10 or 20%. If we are willing to accept a donor that is not matched for all of the genes, then we may find donors for more patients, but those types of transplants are more complicated and that is not preferred. Gore It sounds like there are some patients who just cannot find donors. Seropian If we do not find a donor through the registry in a volunteer unrelated donor, there are other choices to perform transplants, one of those choices is umbilical cord blood. Umbilical cord blood is stored at the time of delivery of a child and that is a rich source of stem cells, concentration of the stem cells that we require is high in cord blood. Unfortunately, cord blood products are small volume, meaning the absolute number of stem cells is not very high and what that means practically speaking is cord blood is a very good graft source for very small patients, namely children, and it is used in adults and that is a very specialized manner of transplantation that is not done in every center, in adults particularly in a normal or larger adult, sometimes 2 cord bloods are required to ensure engraftment. That is one way that a transplant can be performed if we do not have a matched sibling or a matched unrelated donor. Another alternative that is becoming increasingly more popular is the use of family donors that are not matched. In families, if siblings are not matched, they are often half matched and this has to do with the way the genes are inherited from our parents. Now, half matched transplants used to be very difficult. There were significant problems with rejection of the graft because the patient's immune system, even though it is treated is part of the transplant procedure, may still be strong enough to reject a graft that is very different from the patient. And the other problem which has always been limiting has been the risk of the donor's immune system making the patient ill and that is called graft-versus-host disease and that used to be a limiting factor using donors who are very mismatched. In the last 15 years, there has been a lot of work with a new method to try and prevent that problem using a special chemotherapy drug

that is administered after the transplant, which is a very novel and different way to prevent the immune complications of that procedure, it turns out to work very well and so many adult centers feel that is an optimal choice if we do not find a well-matched donor, to turn to a family member who is half matched and then perform the transplant really with a different method to reduce the risk of the complications. Gore Then can those people find donors now? Seropian So, with those two alternate options, most people find a donor. I should mention that siblings are often half matched, but children and parents and even cousins, aunts and uncles can be half match, so that really expands the potential donor pool. It is unusual not to be able to find a donor of that nature within a family nowadays. Gore That is great. So then, all these patients who require a transplant find a donor and then they are cured, is that right? It is curing everybody? Seropian It depends on the disease, and that is not always the case, unfortunately. Transplantation works very well in patients who are in remission, particularly if it is at the time of their completion of their initial therapy, so the complete remission in a patient with a standard leukemia, if he has a well-matched donor, is cured more than half the time and a general statistic is that without a transplant, the regular chemotherapy might cure somewhere between 30 and 45% of those patients. The cure rates are increased with our most common situations where we perform transplant. I think for some of the patients that were choosing alternative donors because we feel like we do not have other good options and those patients do not have a chance for cure without a transplant, the cure rates for those patients may not be over 50% but it may be close in some situations. Gore Is there anything being done or studied to try to improve the cure rate for these rare scenarios? 22:19 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0304-Podcast-Seropian_328701_5_v1.mp3 Seropian There is a lot of research trying to improve the outcome for most cancers as you know, and while there is a lot of that research being done around methods to improve transplantation outcomes, there are a lot of major advances that have come along in treating these diseases based on the understanding of the biology of the diseases. Now we have oral drugs or pills that the patients take for leukemia that can induce remissions, which is really quite striking and many of these treatments have not necessarily cured those patients but have allowed for better control of their diseases and in many case allowed for them to proceed safely with a transplant, and so I think the combination of a lot of these new medicines given either before and sometimes after transplantation is really the way of the future in terms of improving the cure rates. Gore Are there any specific things that you are particularly excited about that is coming down the pike or you are studying? Seropian There is a research trial that we have at Yale that we are excited about. There is one new agent being used to treat stubborn leukemias or refractory leukemia, and I should mention as a general rule transplantation really does not work very well in leukemias that are not already in pretty good remission, so it is really a standard requirement that they have a pretty good response to that chemotherapy in order to proceed with transplant, but that is not always the case – many patients either relapse

after regular chemotherapy or do not go into remission and trying to do a transplant under those circumstances is really quite difficult and so it is more dangerous, but those unusually result in cure. There is a new agent that combines an antibody with radiation, which is a common component of transplantation treatment, but in this case, the radiation is targeted to the bone marrow and the leukemic cells and so a good agent to treat leukemia is now available on a study to focus the radiation to the bone marrow space and to the leukemia and then proceed with a transplant in patients who really have not responded very well to their standard chemotherapy and that is a trial we are participating in because we are enthusiastic and it offers a chance at curative therapy whereas such patients would probably receive alternate chemotherapy in an effort to just keep trying to get them in a better remission and that often fails. Gore Here you are saying that the antibody for a standard cure is radiation to the cells which are not in remission and I guess kills them so that then you can give the donor product, is that correct? Seropian Yes, that's correct. It is given intravenously. All our people envision radiation as something that is administered in the same fashion that people go for x-rays or CAT scans. This is formulated with an antibody and it is given intravenously. It does require some special care in isolation for a few days in the hospital, but that is done a week before the admission for the transplant. 26:04 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0304-Podcast-Seropian_328701_5_v1.mp3 Gore And what happens to their radioactivity in the body? Are the people glowing? Seropian They are not glowing, but it is detectable and that is why they have to be in isolation for a few days and the radiation is monitored until it is down to a safe level and then they can be discharged. Gore That sounds interesting. You mentioned that there are some medicines which are being given either with a transplant or after transplant to help the transplant work better? Seropian That's correct. We know, despite our hopes, that transplant may cure half of patients, sometimes more than half of patients, but there is still a considerable portion of patients who may relapse after a transplant, so we are trying to incorporate some of the newer drugs that are active for cancers – lymphoma is a good example. The most common kind of lymphoma is called large cell lymphoma and we have good treatments for that disease. In many patients, we cure with chemotherapy, but patients who do not go into remission or who relapse often come to a transplant, and in that disease, autologous transplant, meaning we use the patient's own cells, is a common procedure. There is a trial that we have activated where a new oral drug that targets the lymphoma cells is given to the patients after the transplant to try and keep people in remission. That is another example of combining new things with some of our older therapies trying to improve the cure rates. Gore It sounds like you need to work very carefully with the initial or primary treating oncologist or hematologist to put together a big picture of how the transplant fits in and then what kind of monitoring was done afterwards. Seropian That's right. We do share care of patients with the referring hematologist and oncologists and there are a lot of moving parts in terms of collecting stem cells, timing of transplant, but I think it is also

communication that is important so that treating physicians know these new types of therapies are available and some of them have to be given in a certain time point in the course of the disease or they may not be available. And of course, the clinical trials are important because we may be using established agents, but if we are combining in a new way, we do not know if there might be different side effects and of course performing trials in a structured manner really allows us to determine if they work, if they are beneficial because there is always a possibility that combining things may increase toxicity and not change the outcome compared to our standard therapies. Dr. Stuart Seropian is an Associate Professor of Hematology at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at 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.