



Stem Cell Transplants for Pediatric Patients

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Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it is a conversation about stem cell transplants for pediatric patients with Dr. Niketa Shah. Dr. Shah is an Assistant Professor of Pediatric Hematology and Oncology at the Yale School of Medicine and Director of the Pediatric Bone Marrow Transplant Program. Dr. Gore is a Professor of Internal Medicine and Hematology at Yale and Director for Hematologic Malignancies at Smilow Cancer Hospital.

Gore I think one of the first things that I would like to talk about just because it is confusing to I think physicians as well as patients, is bone marrow transplant vs. stem cell transplant – same, different, what's the story?

Shah In general, stem cell transplant is the main word we use and under that category we use the bone marrow transplant, cord transplant or peripheral stem cell transplant. It is the different cells which we use, but they all are stem cells.

Gore And what is a stem cell?

Shah Stem cell is a hematopoietic.

Gore Hematopoietic, what does that mean?

Shah Hematopoietic means these are the cells which produce our blood cells. When I explain to the parents, I say that these are the grandparent cells and the baby cells are produced and these are the red blood cells, white blood cells and the platelets, which run in the blood.

Gore So, the stem cells give rise to everything else?

Shah Yes. The stem cells give rise to everything else and the stem cells have the capacity to regenerate and make all the baby cells. So, that's what term we use for stem cell transplant or hematopoietic stem cell transplant. Now, these stem cells are mainly located in our bone marrow; however, when the babies are born, the placenta also carries the cord blood and the cord blood also has the same capacity as the stem cells. So, sometimes we use this cord blood.

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Gore Cord blood meaning umbilical cord?

Shah Yes, it is the umbilical cord.

Gore Okay. So, you can get stem cells which are found in the blood that is in the umbilical cord?

Shah Yes. They carry the same characteristics as the bone marrow stem cells.

Gore I see. And what about this peripheral blood stem cell thing?

Shah Sometimes it is difficult to collect the bone marrow directly from the bone, so we do give the donor or if we are using a patient's own bone marrow, we give the patient an injection called growth factor for the stem cells, which will generate more stem cells and they will come into the circulation and we collect it from the periphery. That's why we use the term peripheral stem cell.

Gore I see, but they all at the end of the day are giving back stem cells and the stem cells are basically the same, is that right?

Shah Yes. These are all the stem cells. In general, bone marrow transplant, cord blood transplant, peripheral stem cell transplants are called hematopoietic stem cell transplant.

Gore I see. And why would somebody need one? Don't people have plenty of stem cells to go around?

Shah Yes, they have plenty of stem cells to go around, but some of the patients, these stem cells are diseased either due to some genetic diseases or due to some acquired disease like leukemia or aplastic anemia where their stem cells are not working well and they produce bad red blood cells or white blood cells or platelets, so to cure them we use stem cells from a different person.

Gore So, you just collect the stem cells and inject them? That sounds pretty easy.

Shah Yes, it sounds easy but it is not because first we need to find out who is the best donor. And that we do with the help of the HLA testing, which is called human leukocyte antigen testing. And usually, there is a chance that you match your HLA with siblings, but it is not 100%. There is a range of 25-30% chance that you will match to your

4:42 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0120-Podcast-Shah_349887_5_v1.mp3

siblings. However, in the general population, you may match to your same ethnic background population. If you do not have a sibling match, you go to an unrelated donor and find a donor from that unrelated donor registry. In the United States, we have the Be The Match unrelated donor registry, which was started in 1986 and now in the registry, there are more than 19 million donors.

Gore So, everybody can find one that way, is that right?

Shah It should be but it is not like that. Because even though in the registry there are more than 19 million donors, 70% of the donors are Caucasians, so for a Caucasian patient, there are 70-80% chance to find a fully matched donor in the registry if they do not have a sibling as a donor; however, for other minority groups – Africans, Asians, Hispanic, their representation in the unrelated donor registry is not as high as Caucasian donors. So for them, we are sometimes facing difficulty. However, to overcome this issue, we are recommending, and Be The Match is also doing, unrelated donor drives to encourage these minority groups to register.

Gore This would be a targeted drive to a particular ethnic group?

Shah Yes, and we also see that whenever there is a patient from those groups and the family sees there is a difficulty in finding a fully matched donor, the family also tries to do the drive in their local religious or local groups so that there is increased representation in the registry. And it helps us in finding a donor for the future patients.

Gore I see. Well, what about if a patient cannot find a donor in the registry?

Shah Nowadays, we have the option of using the cord blood from the public cord blood bank. So, in the public cord blood bank right now, there are more than 300,000 units, cord units, which are donated by the pregnant ladies after their babies are delivered and they are screened to make sure there is no infection and we have good stem cell numbers and they are already frozen. So, if the patient does not find a good donor, then we go to this unrelated cord blood bank and try to find a donor from there.

Gore But if there are 18 million on the main registry and you cannot find a donor, what is the chance of your finding a donor out of 200,000 units of cord blood?

Shah Yes, that's a very good question and yes we do find difficulty at that front also. However, with the cord blood, there is one advantage – because it comes from the babies, we don't need to go to that highest level of resolution to find a 100% match in the cord. So, even if it is 80 or 90% match at the cord level, we can use those cords.

Gore That's good enough?

Shah Yeah. Nowadays, however, we have another source also. Because each child has their parents, so recently in last 5-6 years, we are doing more and more haploidentical transplant.

Gore What does haplo mean?

Shah Haplo means it is a half match. Because each child is half match to their father or mother because each child carries half genes from father and half genes from the mother. So, we have changed some of our transplant techniques to get the best donor and so whatever the available donor is and use that donor's cells, so even if it is 50% match from the father or mother, we can use those but give some different medicine so that there is no more complication.

Gore I see, and that transplant works as well?

Shah Yes, that works as well. So, whenever we select the donor, yes our first best option will be the sibling; if we do not have a sibling, we go to unrelated donor registry and try to find 100% matched donor; if not, then either go to cord blood bank or haplotransplant from the father or mother, and recently we also sometimes use even if it is instead of 100% match in the unrelated donor registry, if we get even 90% match from the unknown donor registry, that is also good enough. Again, we change a little bit of our techniques on how we do the transplant.

Gore I see. So, now you have got the donor, that sounds like that was a pretty hard thing, so then you just go ahead and inject the cells and you are done, is that right?

Shah It is not again that easy. Then, we need to make sure the donor is healthy enough and available for our timeline to donate. Sometimes, we also face the challenge that if the patient has leukemia or some of the other conditions where they need transplant right away and the donor available is not ready to donate right away, then we again need to work around that which donor is available in our expected timeline. Once we find out that the donor is available for our timeline, then we do pre-transplant workup on the patient to make sure the patient is also healthy enough to tolerate the transplant process. And also make sure the donor is healthy enough and does not have infection. So, that takes again 2-3 weeks to confirm that everything is in good shape. So, by doing the transplant, we are not going to harm the donor or not going to transfer some of the

infection if the donor has into the patient and the patient is also good enough to tolerate all the transplant conditioning chemotherapy. So, here I use the word conditioning chemotherapy, that means we need to prepare donor.

Gore How do you do that?

Shah And that we do because we need to remove the patient's own bone marrow which is diseased and affected and also we need to make sure once the patient receives the donor cells, they are not going to be rejected by the patient.

Gore Okay. So, you treat them with chemotherapy?

Shah Yes. We use some chemotherapy and in some conditions, we use radiotherapy also and also we use immunotherapy. So, this will create first space within their bone marrow, remove their abnormal bone marrow and make sure the new cells will settle down nicely.

Gore So, you are actually killing the patient's own bone marrow essentially, is that right?

Shah Yes, that's correct.

Gore Wow! And then you get to inject the stem cells.

Shah Yes. So, once everything is ready, the patient gets admitted to our hospital room, which is also again a specialized room with HEPA filter and then the patients receive 1 week to 10 days of chemotherapy and/or radiation therapy and some immunotherapy. And then, we give them the donor cells.

Gore And that's not really injected into the bone right? It is not really transplanted in that way?

Shah No. The donor cells will be just received by the patient like a blood transfusion.

Gore I see. But then now you have got stem cells circulating in the blood, how are they going to get to the bone marrow, or does it not matter?

Shah These new cells, the stem cells, will circulate in the blood for 2-3 days and then they will find the best spot in their bone where they can settle down, like if you are moving to a new city, you go first for house hunting to see where you can settle down, and the same thing for these new stem cells, once they are in the new body, they will move around for 2-3 days and find the best spot where they can settle down and start

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making the new cells. Now, this process takes depending on which type of cells we have used, it takes anywhere from 2-4 weeks. If the cells were collected from the periphery from the donor by giving donor some injection, so these cells will engraft, means settle down, and start working within 2 weeks. If they were collected directly from the bone marrow from the donor, they will take roughly around 2-3 weeks. And if they are cord cells, collected from the umbilical cord, they will take anywhere from 3-4 weeks.

Gore Well, what happens to the patient in the meantime?

Shah So, this time period, this 2-4 weeks' time period, the patient does not have their own bone marrow cells and the new stem cells have not started working, and they also experience the side effects of whatever the chemotherapy and radiotherapy the patient has received. So, they have to face all these challenges and this is the toughest time period for the transplant.

Gore So, is the patient sitting in the hospital?

Shah Yes, the patient is in the hospital in a specialized room where there is less chance of infection because the patient does not have the white cells, so they have increased risk of infection and that can be from bacteria, virus or fungus. We do give them some prophylaxis medicine, but they still develop any of this infection, they have mucositis.

Gore What does that mean?

Shah That means, mouth sores because of the chemotherapy and also they sometimes have the chemotherapy side effects in the form of nausea, vomiting, diarrhea and again, we give them supportive care medicine, so they experience less side effects and all these new medicines, once they have done their job, they need to be removed by the patient's body, and these are removed by the liver and kidney. And the liver and kidney when they are removing these medicines, because they are little bit toxic, they may get irritated. So, we have to constantly make sure the liver and kidneys settle and we check their blood work every day to make sure the liver function and the kidney function are not elevated. And we also give them again some supportive care medicine so they experience less side effects.

Gore Well, sounds like these poor kids are being stuck all the time?

Shah Before we start the transplant process, we give them a central line, so they are not stuck all the time and they are either receiving all these medicines through that central line and that central line can be removed once their whole immediate transplant process is over.

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Gore So, they are not really being stuck?

Shah They are not being stuck.

Gore Oh! This is really fascinating, Dr. Shah. Right now, we need to take a short break for a medical minute.

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This is a medical minute about survivorship. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life-changing experience. For cancer survivors, the return to normal activities and relationships can be difficult and some survivors face long-term side effects resulting from their treatment, including heart problems, osteoporosis, fertility issues and an increased risk of second cancers. Resources are available to help keep cancer survivors well and focused on healthy living. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.

Gore This is Dr. Steven Gore, and I am joined tonight by my guest, Dr. Niketa Shah. We have been discussing stem cell transplants for pediatric patients. Niketa, before we go further with this really interesting procedure, I am hoping you can clarify an issue that I think a lot of our listeners struggle with, our younger women and men of childbearing age, because a lot of times nowadays I hear when women are expecting, when they are pregnant, some of them are being offered the opportunity to collect their umbilical cord blood and store it for a rainy day for their families. That is not exactly the same as what you are talking about on the registry, is that right?

Shah Yes, you are right. And it's the same questions we are faced with multiple times also, even in personal gathering or at a conference many times. The American Academy of Pediatrics has also recommended some of the guidelines.

Gore And what do they say?

Shah As you heard that most of the time we can use the different types of the graft sources for the patient. So, umbilical cord is one of the types, and usually, if you take the hypothetical situation, if your child develops leukemia, right now pediatric leukemia has the highest cure rate; 80-90% of the leukemias are being cured by mainly the chemotherapy.

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Gore Without a stem cell transplant?

Shah Without a stem cell transplant. So, even if the child needs transplant down the road, they may find a donor within the sibling or in the unknown donor registry or you can find a donor within the public cord blood bank. And also, sometimes we use haplotransplant from the parents. In my career as a transplantor, I have not denied any or haven't done a transplant because I didn't have any donor.

Gore I see. So, you are really saving this blood; first of all, the chance of your kid getting leukemia hopefully is very small.

Shah Yes. If in your family there is some hematological or blood disease which runs in your family, then yes, you can consider saving your child's cord for other sibling, but you need to make sure that the child is not having that hematological disease.

Gore Yeah, I was a little worried about that.

Shah That is one of the options. So, if you have something like thalassemia or sickle cell in your family, where in the future transplant, a hematopoietic stem cell transplant will cure your child's disease, then yes, the other siblings cord you can save it to be used in future, but again you need to make sure that kid is not involved with that disease.

Gore It is not free to save the cord blood right?

Shah No, it can range, there is an initial cost and it can range from 1000 to 1500 dollars for initial cord processing and then there is a yearly maintenance.

Gore You have to pay every year?

Shah Yes, it depends again with each private cord blood bank. The other thing which we have noticed is that public cord blood banks are highly regulated, and in the private, there is still not those strict regulations.

Gore The regulation is better I am assuming?

Shah Yes. The regulation is much better because it is regulated by the FACT, Federal Accreditation for the Cellular Therapy, and they regulate all these public cord blood banks. So, as a transplant physician and as a pediatrician, we recommend that you

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donate your child's cord to the public bank so it can be used in the future if your child needs it because it is theirs, but the majority of the time, it will be available for the other kids.

Gore Does it cost money to go into the public bank?

Shah No. You just have to contact your OB/GYN practice and they will connect you with the Be The Match or American Red Cross and there are many public cord blood banks in the United States.

Gore And can any OB/GYN have access to donating the blood or?

Shah Yes.

Gore Almost anybody can do it?

Shah And through Be The Match, which is a website, you can connect also.

Gore Well, that's great to know because I get asked by nurses all the time and they are feeling a lot of pressure, the way the private cord banks are presented to them and I know some of them who have actually spent the money but they did not really understand what they were getting into.

Shah Yes. And if you see the data of those private cord blood banks, if we see last 5 years data, very few have been used also for the child's transplant or something else.

Gore Thank you for helping clarify that, I think that is something a lot of people really deal with. So, one of the things that you mentioned just a few minutes ago, was a little surprising to me. You mentioned that if a family has a genetic blood disorder like sickle cell anemia or thalassemia, you might consider a stem cell transplant. I thought stem cell transplants were just for cancer and things like aplastic anemia.

Shah Yes, stem cell transplant is widely used on the adult side for mainly the treatment of leukemia or for the aplastic anemia, but on the pediatric side, we see there are many diseases which are genetically determined; it can be due to some red blood cell disorders like thalassemia or sickle cell, white blood cell disorders – congenital neutropenia or platelet disorder where there is Wiskott Aldrich syndrome which is one of the platelet disorders, or their bone marrow is not working at all, and these are Fanconi anemia patients also, and here, we do transplant so their diseased bone marrow is replaced, the same way we do the transplant for aplastic anemia or leukemia

and so they have the new healthy bone marrow, which will produce the new cells which are healthy. So, they are not facing any of those issues. And recently, there is a drive towards sickle cell transplant also because for sickle cell disease patients, they face many difficulties because of their sickle cell and it can vary from different patients; some may have less issues, but some may have more issues and the average life expectancy for sickle cell patients is not the same as a healthy adult.

Gore Right. Well, I know that sickle cell diseases are especially common in people of African ancestry, of whom there are many in our listening area and yet transplant for sickle cell disease does not seem like it is very common; otherwise, why would we see so many adult patients who are suffering. Should everybody with sickle cell disease be transplanted?

Shah I will recommend that everyone with the sickle cell disease, if they have a healthy donor option available, they should be screened for the availability and the cure option of this transplant. We have noticed that, yes compared to thalassemia which is another disease which is common worldwide, mainly in the Mediterranean area, almost all patients are screened for the thalassemia because from the age of 1 year, they are transfusion dependent. While on the sickle cell disease side, it is not uniform; some may have as mentioned less complications and so they are not that, but once they cross their adulthood, there are chances that they have more complications. And recently, when we did this survey of all the sickle cell transplants who received transplant from the sibling all over the world, we noticed that the younger the age of the transplant, the higher success rate. So, for a sickle cell disease transplant with the matched sibling, the success rate is more than 90%.

Gore 90%, it cures the disease in 90%?

Shah Yes, and again, if you have done the transplant when the patient age is less than 10 years, the success rate is anywhere from 90-95%. Afterwards, each year you wait, the success rate drops because by that time, either they have received many blood transfusions, they have observed many other complications which affects the success rate of the transplant.

Gore At what age should that be considered for a young person with sickle disease who has a donor?

Shah If they have a donor, any age after 5 years if they have experienced multiple pain crisis, has acute chest syndrome, one of the lung complications which they experience

almost 1 or 2 times a year or they have more blood transfusion requirements or they have a tendency towards developing stroke, then they all need to be offered this option if they have a healthy donor.

Gore But if they are not having symptoms, then would you hold off?

Shah Again, that's debatable. In European countries, even the younger patients are being transplanted. Here, we are doing under the study, it is called the low-risk sickle cell patients and here at Yale, we have opened a study where we are giving the option of if they have a healthy donor available, then at a younger age also we can offer them the transplant. So this way, they are not going to experience any complications because having the sickle cell disease itself, they have a chance of developing all these complications in the future. It may not have appeared at their younger age, but there are chances they will have these complications down the road.

Gore What about long-term problems from the transplants in these very young patients?

Shah So, that is a really good question. And that is what is being evaluated and what we are doing is, if they have the younger age and particularly also for the sickle cell disease transplant itself, nowadays we are not treating them, we are not performing their transplant the same way as we performed the transplant for leukemia patients. So, we are doing what is called the reduced toxicity type of transplant so that they have less complications or no complication because of the transplant medicine, which we use in long term. So, that is the approach and most of the time again, we compare. Previously all these non-malignant disease transplants were also being performed the same way as the leukemia transplant, but nowadays all the non-malignant diseases, particularly sickle cell in itself, we are performing it using the less toxic medicine, and when we compare the success rate, it is similar; plus, they have less side effects in the long run.

Dr. Niketa Shah is an Assistant Professor of Pediatric Hematology and Oncology at the Yale School of Medicine and Director of the Pediatric Bone Marrow Transplant Program. 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.