Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous 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 1-888-234-4YCC. This week, Francine welcomes Dr. Sunil Abhyankar. Dr. Abhyankar is Associate Professor of Medicine and Pediatrics, and Director of Bone Marrow Transplant Phoresis & Cell Processing at the University of Kansas Hospital.

Foss Can you start off by telling us a little about your background and how you became interested in this whole area of bone marrow transplant?

Abhyankar Bone marrow transplant has always been on the cutting edge of oncology and the treatment of cancer. I trained at the University of Bombay, or Mumbai as it is now called, and I was doing pediatric oncology there. We saw a lot of patients with thalassemia in India, and it is quite common in that area of the world and the treatment for thalassemia involves transfusions every week or every two weeks, depending upon how low the hemoglobin is. I used to see many of these young kids and the blood banks were not adequate and did not have all the equipment, and the transfusion needs were quite high and we always thought, wouldn't it be great to have a transplant program here so that we can cure this illness? And that is how I got interested in allogeneic bone marrow transplant, which is a donor type of bone marrow transplant. I came to the US back in 1987 when transplant was not that well established in India, and I spent about three years at Dana-Farber working with Dr. James Ferrara who initially was my mentor and I did research there with him in graft-versus-host disease and then that got my interest into trying to focus in graft-versus-host-disease as a field that I wanted to try to do research on in my clinical work to see how we could decrease that complication after transplant. Originally my interest was trying to cure thalassemia in pediatric, or young children, with this transplantation.

Foss It is a bit unusual for us to think about using bone marrow transplant for something other than leukemia or lymphoma. Can you just let the audience know what thalassemia is, for those of us that may not have heard that term and can you talk about the role of bone marrow transplant in treating those non-malignant diseases?

Abhyankar Absolutely, thalassemia is a genetically inherited condition. It is a recessive inheritance and it was first described in the Mediterranean regions,

so it use to be called Mediterranean Anemia, and it was common in Italy and Greece, and as you know, India has a wide genetic pool because people have come to India from all over Eastern Asia and Western Asia, so there is a big population of patients who have inherited this gene and now this is recessive inheritance. You have to have a part of the defective gene inherited from the father and another part inherited from the mother and when the two come together in a child, that results in a condition where the hemoglobin formation

3:59 into mp3 file http://yalecancercenter.org/podcasts/2011_1030_YCC_Answers_-_Dr_Abhyankar.mp3is not as effective. The hemoglobin that forms when the baby is born is a fetal hemoglobin, but as the baby gets older, the child gets older, it converts to adult hemoglobin and with this particular genetic condition, the formation of adult hemoglobin is defective, so what happens is the child becomes anemic. Typically in a severe case of thalassemia, the parents bring the child because the child looks very pale and it usually happens around four to six or seven months of age, and we start testing and then we determine what the problem is, that the baby is not making enough hemoglobin, the bone marrow has no sub cells, the cells are trying to make the hemoglobin but because the gene is defective, the hemoglobin molecule is not formed in a proper fashion and then that results in severe anemia. The only way you can correct that is by giving transfusions. Thalassemia is not very prevalent in this country, although it is seen in the Northeast where you have people who are from Mediterranean ancestry and we have to have two individuals who carry that gene that have children and the children inherit that disease. So, you do see it in the Northeast, but in India the problem is that the blood banks do not have a good source of voluntary blood donations. So, a typical family, let's say they unfortunately have a child with thalassemia, then they have to line up people who would be willing to donate blood for their child and this is a life long process because there is no cure for this illness. In those countries, transplanting and doing a bone marrow transplant where basically we are replacing the defective bone marrow of the patient with a healthy bone marrow from a match individual, usually it is a sibling who is match, will cure that inherited disease in the bone marrow and the inheritance of the disease only affects the bone marrow, it does not affect anything else in the child. The children grow well, the hemoglobin stays normal, they are very bright young kids they have nothing wrong with them. It is anemia that, if not properly managed, can then cause a lot of problems, growth is stunted and then the spleen becomes big, the liver can become big to compensate for the anemia and that results in multiple other problems. A good way to manage thalassemia in this country, because we have excellent blood bank support and the blood is screened for all infectious agents, is transfusions to maintain a hemoglobin around 9 or 10, in that range, and then that will prevent the child from having the effects of chronic anemia which would include stunting and all the physical affects that go with chronic anemia.

Foss Typically we think about bone marrow transplant in the context of adults, but you are coming at this from a pediatric point of view. Can you talk a little about what the differences are between adults and children in terms of the whole process of bone marrow transplantation and the success of the procedure?

Abhyankar Yes, I forgot to answer one of the previous points in your previous question. Typically, in adults we are using the transplants for treatment of malignant or a cancer condition, but there are a lot of non malignant conditions for which we do bone marrow transplant as well, and many of these are in children. One I mentioned is thalassemia. There is some evidence that in some patients with sickle cell anemia they can benefit if it is done in the right context, in the right population, and the

8:05 into mp3 file http://yalecancercenter.org/podcasts/2011_1030_YCC_Answers_-_Dr_Abhyankar.mp3right donor. Similarly, there are inherited immune disorders. The only way you can cure those is by replacing the bone marrow stem cell from a healthy donor, and there is another condition which can be acquired which is called aplastic anemia where the patient's bone marrow does not make any cells, white cells, red cell, platelets, and sometimes this did not respond to suppressing the immune system, and if you have a well matched donor then we would do a bone marrow transplant with a very good success rate. Those are the non-malignant conditions for which the bone marrow transplant can be done, in brief, but getting back to your next question about what is a major difference between adults and children when we do transplantation for these inherited diseases, or these acquired cancers. The major difference is that in children they seem to recover better from all the chemo that we use to do the transplant. By the way, bone marrow transplant is often interchangeably used with stem cell transplant because the stem cells that we collect to do the transplant come from the bone marrow. So, we can either get these stem cells from the bone marrow physically, or we can get stem cells from the peripheral blood by making stem cells come out from the bone marrow into the blood and then harvesting it from the blood. The words can be interchangeably used sometimes, but the main way we have to do the transplant is first we have to give a big dose of chemotherapy, sometimes combined with a big dose of radiation, so that whatever condition that the patient has, whether it is a leukemia or a non malignant immune defect, then you want to suppress or kill some of those bad or defective immune cells just as you want to kill the bad cancer cells that might be in the bone marrow. Often we end up using an intense regimen of chemo and radiation and that is followed by infusion of the bone marrow or the infusion of the stem cells that have been obtained from the blood. Children are able to tolerate these treatments better

and they recover faster than adults. As we get older our ability to tolerate these more intense chemo regimens goes down and children recover faster from that. There is also a complication called graft-versus-host disease where the donor cells attack the recipient. It is like the opposite of rejection. In rejection, the patient rejects the donor stem cells, but in graft-versus-host disease, the donor cells begin to attack the patient's tissue because they realize that they are in a different body even though the donor and the patient are well matched, and that is called graft-versus-host disease. That complication is much less in the pediatric age group and more and more now we are doing transplants in 70 and 75-year-old people, and in that situation we see that there is a much higher risk of graft-versus-host disease. Overall children recover faster from the bone marrow transplant, the cure rates of some of these diseases is higher in children than in adults, mainly because the immune system is a little bit naïve compared to the older person's immune system, and therefore, they seem to have less complications. But getting a child through a transplant is a pretty intense process and that is because you have to deal with the young mind and young child who may not completely understand what is going on and it involves a lot of support from the parents and it involves a lot of support from social services, the child psychologist, the therapist, and you need to have a very dedicated team and dedicated group of individuals. It is not just the physician. The physician's role is quite small in actually doing this process, we have to

12:24 into mp3 file http://yalecancercenter.org/podcasts/2011_1030_YCC_Answers_-_Dr_Abhyankar.mp3 have a big team to help this child get through the transplant and help the family get through the transplant.

Foss At the University of Kansas you are a regional center and patients travel from very far to get to your center, much like the North East where we have many centers. Can you talk about what the experience is like for a patient? How do they get there? How long are they in the hospital? And what happens when they get discharged?

Abhyankar A very good point, you are absolutely right because the transplant is not something that is being done in the community centers, and it should not be done in a community center, obviously. The patients do come from far away. In the Kansas City area where we are located we get patients all the way from Western Kansas which is about 400 miles away. We are very lucky because we have a bed and breakfast kind of place that is run by the American Cancer Society. And the patients who are coming from far away can stay there free of charge for almost 100 days, for the duration of the transplant. Typically, when the patients come from far away we except that they stay in the area, around a

10 to 15 mile radius for about 100 days post transplant so we can watch them for complications.

Foss We are going to take a break right now for a short medical minute. Please stay tuned to learn more about bone marrow transplant with Dr. Abhyankar.

Medical

Minute Breast cancer is the most common cancer in women. In Connecticut alone, approximately 3,000 women will be diagnosed with breast cancer this year, and nearly 200,000 nationwide, but there is new hope for these women. Earlier detection, non-invasive treatments, and novel therapies provide more options for patients to fight breast cancer. In 2010, more women are learning to live with this disease than ever before. Women should schedule a baseline mammogram beginning at age 40, or earlier if they have risk factors associated with the disease. With screening, early detection, and a healthy lifestyle, breast cancer can be defeated. Clinical trials are currently under way at federally designated comprehensive cancer centers such as Yale Cancer Center, to make innovative new treatments available to patients. A potential breakthrough in treating chemotherapy-resistant breast cancer is now being studied at Yale combining BSI-101, a PARP inhibitor with a chemotherapy drug irinotecan. This has been a medical minute, brought to you as a public service by the Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

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Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and today I am joined by my guest Dr. Sunil Abhyankar. We are here discussing bone marrow transplantation and we talked a little bit in the first half of the show about pediatric bone marrow transplantation, particularly for non-malignant diseases such as thalassemia. However, most of our patients, at least in the adult setting, have various kinds of leukemia or lymphomas. You touched a little bit on some of the differences in children, can you briefly talk about some of the differences between a patient with leukemia and lymphoma getting a transplant versus a child who is otherwise well with sickle cell anemia or thalassemia. Is the transplant more complicated and are there more complications as a result of the process?

Abhyankar Those two groups of diagnoses are quite different when we approach how we do the transplant, so, if for instance you have a child with thalassemia, or sickle cell who does not have underlying issues, there is no malignancy or cancerous condition involved, and it is a genetically inherited defect in the red blood cells, often that child has been transfused to keep up the hemoglobin, and when somebody gets multiple transfusions, the iron that is there in the blood of the transfused blood can accumulate overtime and this iron gets deposited in our tissue, in the liver, in the heart, and other areas and that can cause serious problems. So, before we take somebody to transplant for conditions like thalassemia or sickle cell anemia, we have to estimate how much iron overload that person has because that can significantly impact what the outcome of the transplant is. The other issue is that every time we transfuse somebody with blood there is a risk that they can develop antibodies to the different red blood cell antigens and can get sensitized to different red blood cell product and then this can create a situation where there is higher risk of rejection of the stem cells from the donor. Whereas when you look at a condition in an adult lets say with a leukemia or a lymphoma and you are looking at doing a donor type of transplant, not autologous transplant, that is really a different situation. There is some urgency going into transplant. We need to workup the patient quickly. We need to identify the donor quickly and the research done in this country has shown that many times what happens, unfortunately, is that the right donor is not found in the right time and if you look at the statistics of how many people actually need to undergo transplant versus how many people undergo transplant there is quite a gap and that gap is because we cannot find the right donor, or if the right donor is found, the donor has not been able to donate the stem cells in the right time that is needed. So often what can happen, as we are waiting for the donor to materialize, the patient may relapse and that cancer may come back and now we are giving other therapies to try to put the cancer in remission before we do a transplant. So, there is a complete different approach if we have a non-malignant condition like thalassemia, sickle cell, as compared to a malignant condition where there is more urgency. Also in a malignancy there is more exposure to chemotherapy that this person has had before they go to transplant. So, the transplant related complications that occur because of exposure to

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chemotherapy, we see more in that particular group than in the other group where they have not been exposed to any kind of chemotherapy before we undergo the transplant process.

Foss So the best donor obviously would be a sibling who identically matches the patient, but as you said, we do not find that that often. Can you

talk about some of the alternative types of donors that were using now and how successful those transplants are?

Abhyankar Absolutely, so the chance that a sibling is a match is about 25% and this is simple genetics. So there is a 75% chance that the person does not have a match in the family. In that situation we have to look for donors either through the donor registry. Something exciting that has started happening over the last few years is the availability of umbilical cord blood and the ability to do transplant using umbilical cord blood. But getting back to donor registry, the donor registry is run by the National Marrow Donor Program and the National Marrow Donor Program in this country is linked to the donor registries in Europe and other countries around the world so there are about 13 or 14 million people in all these registries who are registered to volunteer to be a donor for somebody who needs a transplant. It is common that if a patient's brother and sister do not match, and that patient happens to have a Caucasian ancestry, or mostly European ancestry, we are able to find a donor through these 13 or 14 million donors and there is almost a 70% chance that we find a donor through the donor registry, but if the patient's ancestry is not Caucasian or European, but is a mixture from India, lets say, like me, the chance that somebody like me will find a donor through the donor registry is quite small. I heard a statistic in one of our bone marrow transplant meetings, that to find a donor for a person with a Caucasian background you would need to screen about 20,000 people, but for somebody with East Indian background or even American Indian background, we would probably need to screen 80,000 people of that ethnicity and that is because there is more genetic diversity in people who have come from India, similar in people of African-American descent and, therefore, it gets very hard to find a donor for the person you would call a minority in this country through a donor registry. They have higher genetic diversity and also the number of people volunteering to be on the donor registry is small in these communities. In this situation there is exciting research now and clinical research showing that umbilical cord blood can be used to successfully do the transplant and cord blood banks around the country have been banking cord blood now for many years and they have now big stores of cord blood. What can happen is a person needs a transplant for leukemia, and let's say they are of East Indian descent, we cannot find a sibling match, we do not have a donor through the national National Marrow Donor Program, so we quickly look at the cord blood and what cord blood is available. The advantage of cord blood is that you can successfully do the transplant even with a miss match situation. Normally when you do a transplant you have to match a different human leukocyte antigen located on the DNA. We call them HLA, or to use another word, a tissue type. So, we

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have to match 8 different locations on the DNA and we say the person is a perfect match when

they have 8/8 match. Whereas when you look at the umbilical cord blood you do not have to have a perfect 8/8 match. In the cord blood situation we are looking at 6 different locations of the DNA and these are at A B and DR and so in the cord blood you could have only four out of those six matches and be able to do a successful transplant. So, the choice of donors is increasing now because of available cord blood. Similarly, haploidentical transplant is also being done more frequently. Haploidentical means half match. So let's say somebody has a sibling who is not a match, but all of us will have half match siblings. If our brothers and sisters are not a complete match genetically with us for purpose of the transplant, they will at least be 4/6 or 3/6 match. In that situation, we can use a sibling donor, if we have haploidentical program or a protocol to be able to do this transplant. These are still being done under research studies so this is not something that is yet mainstream, but cord blood and haploidentical transplants will expand the donor availability especially for people of ethnic minority in this country.

Foss The major complication as you do more and more mismatched is graft-versus-host disease, as you touched on earlier. Can you talk a little bit about the management of graft-versus-host disease and some of the new things that you have been working with?

Abhyankar Graft-versus-host disease, as you rightly mentioned, is a major complication of bone marrow or stem cell transplant from a donor and this happens because the donor's immune system recognizes that they are in a foreign body and begin attacking different tissues. Typically when graft-versus-host disease occurs, the tissues are involved at the skin, GI system, the liver, and in a long term situation, it can also attack other organs like the musculoskeletal system, the lungs and other tissues. Graft-versus-host disease can be pretty devastating and therefore, when we do transplant, we try our best to limit the amount of graft-versus-host disease that occurs. We do not want to completely get rid of graft-versus-host disease because what we know from research is that a little bit of graft-versus-host disease is beneficial because when the donor's immune system fights the patient, it also fights the patient's cancer, and therefore, we want a little bit of graft-versus-host disease, but we do not want it to go out of control. If you were to look at just incidence of graft-versus-host disease, it can vary anywhere from 50% to 70% of the time after the transplant and it all depends upon how good the match is between the donor and the patient, how old the donor is, how old the is patient and then certain other things like infection like CMV, which can contribute to the development of graft-versus-host disease. There is a 50% to 70% chance that somebody may end up with GVHD. So, after we do the transplant we have to use medications, immuno-

suppressive drugs, to prevent this complication if we can and then if it does happen the main stay of treatment for GVHD is the use of prednisone and as you may know, prednisone is a drug used to treat many immune disorders, and also GVHD, but it does have a lot of side effects,

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tremendous side effects causing diabetes, hypertension, muscle weakness, osteoporosis, and many others. So, the research has been focusing on trying to limit how much prednisone we need to give to somebody who develops graft-versus-host disease and there are many other agents that have been tried. One that I am particular interested in is not really an agent but is a therapy called photophoresis, where the patient's white blood cells are collected in a special machine and they get exposed to ultraviolet light in the presence of a drug, which is called a photosensitizer and what happens then is that the photosensitizer drug in the presence of UV light damages some of the DNA and some of the cells and when these cells get infused back into the patient then this sets up a process by which we generate what we call immune tolerance, that means the generation of tolerance between the donor's immune system and the recipient of the patient's tissues and immune system.

Foss I was just going to ask you how well this whole treatment works, and how successful it is?

Abhyankar We would like it to be more successful and unfortunately there is no panacea in the treatment of GVHD or preventing GVHD, but it does work when somebody has graft-versus-host disease and it does work about 30% to 50% of the time and the advantage of this particular treatment is that we have very few side effects and therefore, somebody undergoing GVHD treatment, if this treatment is working, we can successfully wean or taper off the other immunosuppressive drugs.

Dr. Sunil Abhyankar is Associate Professor of Medicine and Pediatrics and Director of the Bone Marrow Transplant Apheresis and Cell Processing at the University of Kansas Hospital. If you have questions or would like to add your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.