Pediatric Stem Cell Transplantation

Guest Expert:

Deborah Chirnomas
Assistant Professor of Pediatrics at Yale School of Medicine and Director of the Pediatric Bone Marrow Transplant Program at Smilow Cancer Hospital

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. I am Bruce Barber. 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. Deborah Chirnomas. Dr. Chirnomas is Assistant Professor of Pediatrics at Yale School of Medicine and Director of the planned Pediatric Bone Marrow Transplant Program at Smilow Cancer Hospital. Here is Francine Foss.

Foss Let us start off by talking a little bit about you. You are new to Yale Cancer Center, can you tell us where you came from and what your background is?

Chirnomas Originally, I was in medical school in New York, and then I started my medical career at Yale as a pediatric resident and then I moved to Boston for a few years to do a fellowship in pediatric oncology at Dana-Farber/Children's Hospital. Then I had a great opportunity to come back and was very excited to do so.

Foss When you came back here, Yale Cancer Center did not really have a bone marrow transplant unit, and we still do not, for children. Can you talk a little bit about that and what your plans are?

Chirnomas Currently, in the State of Connecticut, there is nowhere for a child to get a bone marrow transplant if their therapy requires it, so they need to go either to New York or to Boston or to various other cities. This is really a tremendous hardship on families because the transplant itself is a very long process, and so Yale has decided that it was time to rectify that and allow for families to stay local.

Foss For the sake of our audience, could you explain a little bit about how you become a pediatric transplanter, so first you are a pediatrician?

Chirnomas You go to medical school, became a physician, then you train in pediatrics and then you do a fellowship, which is several years in pediatric hematology/oncology, and that includes specializing in bone marrow transplant, and then I spent several more years working almost exclusively doing bone marrow transplants in Boston.

Foss Can you tell us the most common kinds of cancers in children that would lead to a transplant?

Chirnomas The main kind are the leukemias, so acute lymphoblastic leukemia, otherwise known as ALL, also acute myeloid leukemia, AML, and in addition several solid tumors, the most common being neuroblastoma.

Foss Are these, in fact, the most common cancers that children develop, in general?

Chirnomas The leukemias are, ALL is the most common childhood cancer accounting for about one-third of

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pediatric childhood cancers. However, neuroblastoma is a fairly rare disease. Childhood cancers, in general, are rare.

Foss In terms of looking at children overall with cancer, how do these children usually present?

Chirnomas It obviously depends on the disease. There are many kinds of cancer, and so there can be many different presentations. What I would say is there are some classic signs for leukemia including being very pale or bruising easily, maybe complaining of bone pain, but those are very general symptoms that frankly apply to every teenager and many other children. The best advice I can give to parents is if something is wrong, if something is off, and your children are not right either because they are not eating right, growing properly, not doing their normal activities, any out of the normal things that strike you, you should bring your child to a healthcare provider. It will almost definitely not be cancer, but a parent’s radar is really the most important thing that we count on, and then we take it from there.

Foss I know in adults that a lot of patients present to a doctor for another reason and they are found to have cancer. How often in children is cancer diagnosed, say, incidentally, when something else might be going on?

Chirnomas That is really quite unusual. Children are so often well that they do not present for a lot of other reasons. Having said that, it is common to hear a story that, oh, my child was hit with a bat at practice and then we noticed a lump. A lot of times the family will find things because there is a part of a body that they all of a sudden have their attention brought to. That is as close to an incidental finding as you would see, I would say.

Foss And most children who present with leukemia, do they present specifically with signs related to the low blood counts or are they also asymptomatic?

Chirnomas They do usually have symptoms of low blood count or high blood count. Again, they can look very pale if the red blood cell count is low and they are anemic. They might have bruising because their platelet count, which comes from their bone marrow, is low. They may have those symptoms. Again, I just would emphasize that it is all very rare, and so those symptoms can appear in many other settings, but we do often see that for leukemia.

Foss Are there any specific age groups where these diseases are more common?

Chirnomas Absolutely, the two clusters are really 5 years old and under. In fact, the highest likelihood of cancer occurring is really by the age of 1, and then the second cluster is between ages 15 to 19.

Foss So, under age 5, and then in the teenage years?

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Chirnomas: Exactly, and in the teenagers, it is really not leukemia, it is more like lymphomas, things like Hodgkin’s lymphoma or non-Hodgkin’s lymphoma, that are more common.

Foss: And the neuroblastoma?

Chirnomas: Neuroblastoma is actually also common in those two age groups, much more so in 5 and under, but we do see another little peak in the teenage years.

Foss: How are pediatric cancers diagnosed? Is it usually diagnosed before you as a medical oncologist see the patient or do you oftentimes make the diagnosis?

Chirnomas: It is a combination. I think that pediatricians are usually the first people to see the child and notice that something is not right, they may do a blood count and the blood counts are not normal, or they examine the child and see a lump or feel something in the belly. So, often, the pediatricians pick up on the first signs if something is not right, or the child might even be in the emergency room, but then we usually need to make the actually diagnosis.

Foss: Do many of these children present to you, say, with lumps, without a diagnosis?

Chirnomas: Yes.

Foss: And then you move forward with the work-up.

Chirnomas: Exactly, and that usually includes some blood work. Sometimes, if there is a lump, we biopsy it and see what it tells us. That is usually the fastest way to get information. For leukemia, you do not often have lumps or bumps. That is usually just a blood test.

Foss: What kinds of staging tests are used for children? I know in adults we do PET scans, CAT scans, and bone marrow biopsies. Are PET scans used in children as well?

Chirnomas: They are, and it is with increasing frequency. Everything in pediatrics, we are always risk averse. We wait until everything is sorted out in adults and then we kind of jump on board when we think things are safe. We are using PET scans and their role in any given disease depends on that disease, but certainly for lymphomas, even for leukemias, we are starting to use them more for staging and also for surveillance afterwards.

Foss: If a child is diagnosed with a cancer, or there is a suspicion of a cancer, how difficult is it in the State of Connecticut to find a pediatric hematology/oncology physician?

Chirnomas: It is actually not that hard. There are two really main hubs at CCMC and Yale, and so most pediatricians are able to pick up a phone and call one of those centers. At Yale, we have outlying...
facilities where people know how to reach us. It is a matter of one or two phone calls. People are pretty able to access a physician.

Foss For children in Connecticut who need a bone marrow transplant, they are not done in the state, I understand. They are sent to other states?

Chirnomas Yes.

Foss And your goal here is to develop that program?

Chirnomas Yeah, it is a very exciting opportunity and hopefully for the families of Connecticut as well. Yale has decided to invest in making this a premier program and a place where families can feel very comfortable getting excellent care for their child without having to leave the state.

Foss As a potential bone marrow transplant center, would you be seeing these patients at the beginning of their diagnosis, or only at a certain point when it is determined that a transplant would be necessary?

Chirnomas That is a great question. In general, as a transplanter I enter the picture when it is determined that they need a transplant. Many diseases do not require a transplant, and so it would be a little overwhelming to families while they are already dealing with bad news to think about a situation that usually causes a lot of anxiety on top of it.

Foss Out of all the potential cases that you would be transplanting in children, can you tell us what the distribution would be like for what disease, what is the distribution that you would expect?

Chirnomas In a large majority it would be leukemias, either ALL or AML that have relapsed. There are times when you do have children that present with AML and ALL that you would transplant right upfront based on their genetic tests and certain features of their disease. The leukemias definitely comprise the majority and those are usually for what is called an allogeneic transplant. Those are transplants where we use someone else’s bone marrow, either a relative or an unrelated donor, to replace their bone marrow. Neuroblastoma, Hodgkin's disease, and relapsed lymphomas require something called an autologous transplant where we take their own bone marrow while they are getting normal chemotherapy, and then we actually give them high-dose chemotherapy in an attempt to cure their disease, and we rescue them with their own bone marrow, and that would definitely make up a percentage of maybe 20% to 30% of our transplant population. The other diseases that we have not really mentioned yet today are the non-malignant diseases, the diseases that are not cancer, and those include bone marrow failure problems, or diseases, such as aplastic anemia as well as hematologic problems such as sickle-cell disease or thalassemia. In addition, transplant in children is expanding for other indications for certain storage diseases like adrenoleukodystrophy or another one called Krabbe’s disease, etc. These are metabolic disorders where by replacing the bone marrow we believe that we are giving the patients an ability to make

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an enzyme that their body is otherwise not making, and in addition, there are great indications now for immunodeficiencies. These are children that are born with problems with their immune system, like if anybody saw ‘The Boy in the Bubble’ a movie way back, forever ago. I think John Travolta might have been in it. In any case, children who have severe immune deficiencies can often now be cured with a bone marrow transplant, and so I would expect those cases, they are a little bit more rare, but I would except those to make up a portion of our population as well.

Foss Debbie, when you hear the word “bone marrow transplant” at least in the adult setting, we still have people who are really afraid of the whole concept, is that a major issue for you as you move forward and talk with a family about an upcoming transplant in their child?

Chirnomas I think it is for several reasons. It is very scary and they need a lot of education and the words themselves have this mystique that we spent a lot of time trying to go through and demystify, particularly for the autologous transplants.

Foss We will talk a little bit more about some of those details when we come back after the medical minute. Please stay tuned to learn more about bone marrow transplant in children with Dr. Deborah Chirnomas.

Medical Minute There are over 11 million cancer survivors in the US, and the numbers keep growing. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life-changing experience. Following treatment, the return to normal activities and relationships may be difficult and cancer survivors may face other long-term side effects of cancer including heart problems, osteoporosis, fertility issues, and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers, such as the one at Yale Cancer Center, to keep cancer survivors well and focused on healthy living. This has been a medical minute brought to you as a public service by Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by my guest today, Dr. Deborah Chirnomas, and we are discussing pediatric oncology, and specifically, pediatric bone marrow transplant. We talked a little bit about the many indications for transplant before the break, but can you talk to us a little bit more specifically now about the procedure of transplant in children and the potential complications?

Chirnomas Our focus is mostly on the process for allogeneic transplants where we need someone else’s bone marrow because that’s the one that people think about when they think about bone marrow transplant. Basically, in children, the studies have shown us that we require bone marrow from an unrelated donor or a related donor that comes from the bone marrow versus from the arm. In an adult transplant, we can give a medicine and then take the stem cells from their arm, but in
pediatrics, we ask the donor to go under general anesthesia and allow us to take the bone marrow out of their hip bones, and that gets coordinated with the medicine that the patient needs to receive to make their bone marrow go away, and so we coordinate this process, and basically on the same day that they are ready to get their transplant, we ask the donor to give this bone marrow from the back side usually, and then that gets flown from wherever it is, around the world if it is an unrelated donor, or from a sibling, it would be locally. We give that in a bag. It is really quite boring once it actually happens. It looks like a blood transfusion and families are often a little bit disappointed, it is anticlimactic and they say, really, that is it?

Foss Can you talk about the experience for the donor?

Chirnomas In general, what we know is that children, younger children who are donors, do a little bit better. They actually heal -- they do not know they are supposed to be sore and achy, and so they rebound fairly quickly. Most donors find it an amazingly rewarding experience in terms of actual physical issues. They are a little bit sore for a couple of days, and this is based on many interviews and data collected by the NMDP, but in general, it is tolerated very well. People are usually very happy and willing to do this.

Foss Is there a lower age limit for a donor, how young a sibling would you consider?

Chirnomas Often we have infants born that we know we might need to use as a donor and the cutoff age is 6 months. We often ask that if we know there is a baby coming who might be able to help out a child who is already ill, we often ask to save the cord blood, and then when the baby is 6 months, we can then take some of their bone marrow and we combine it with their cord blood and we have enough to use for the child.

Foss In the adult setting, when you use an unrelated donor, you oftentimes have issues with graft-versus-host disease. Is that the case with children as well?

Chirnomas It is, but it gets back to this reason of why we have become very focused on using bone marrow from the hips and not using the bone marrow that you can get from the peripheral blood or from the arm. It turns out that when you use it from the hips, at least in children, we have been able to show that we will get less graft-versus-host disease, but it absolutely is still a big complication that we struggle with.

Foss You talked about the use of umbilical cord cells as well. Will Yale Cancer Center be doing umbilical cord transplants?

Chirnomas In pediatrics, it is the standard of care. It has really opened up a new world of options for children who otherwise would not have donors, and because children are smaller, the umbilical cord, which is often very small, ends up being adequate for many children. It really is a great option. There is

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actually a cord blood bank, which legislation has just passed to fund, in the State of Connecticut. It is a very exciting time for cord bloods in Connecticut. The Kacey Rose Foundation has been very involved in getting this off the ground, and so we will hopefully have a place in Connecticut for people to donate their cord blood.

Foss Can you explain the procedure for anybody out there, say who is pregnant, who might what to donate their cord?

Chirnomas I would be happy to. It is actually a little bit complicated. If you want to donate the cord, not save it for your own family which costs a lot of money, it is generally free. The only thing you have to do is do a little bit of legwork talking with your OB/GYN and getting the kit beforehand. The obstetrician does not have the cord blood kit with him or her. Usually the mother has to get it, which can be done by sending away to one of these companies, such as ViaCord or if you Google it you will come up with many options, and basically if you send away for these kits and bring it with you when you go to have the baby, the obstetrician will collect the cord blood and send it off to the appropriate place, but it is completely free of charge.

Foss Can you talk a little bit more specifically, going back to the whole process that the patient goes through for transplant, we do a number of different conditioning regimens in adults and particularly reduced intensity with less chemotherapy so that the whole process is less toxic, do you do that in children as well?

Chirnomas We do, and it is certainly an area of very active research right now. In general, for the diseases that are cancer-based, we do not do as many reduced-intensity regimens. We find that children tolerate the conditioning quite well and it is really necessary to cure the cancer. For most leukemias, we still are using the more intense conditioning regimen with is total body radiation and cyclophosphamide, or other agents. For some of the other diseases I mentioned such as aplastic anemia or sickle-cell disease, we are actively researching ways to use the reduced-intensity regimens to allow a safer procedure for people who do not have cancer and do not necessarily require the transplant.

Foss Are these transplants done in the hospital, and if so, how long is a patient usually in the hospital for?

Chirnomas In general they are in the hospital. There have been some publications in children where they do autologous transplants outpatient, but in general the model to date has been to do it in the hospital. A child will come into the hospital and the average stay is basically 4 to 6 weeks. The mean time is something like 32 days.

Foss How do children usually tolerate the complications?

Chirnomas Children do very well in general. We have gotten much, much better at supportive care and for

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the children in general their pain is managed incredibly aggressively. Frequently they do not remember that much of it. It is really the parents that we wish we could provide better anesthetic for or amnestic so that they do not really remember it, but it ends up being the families, the parents who get a little bit claustrophobic and it is a long time to stay in one small space trying to watch your child who is not in their best mood.

Foss Can you talk a little bit about the difficult decision for the parents to make a commitment to send their child do a transplant? How do you handle that with the parents?

Chirnomas There is no one exact way. The main way we do it is with lots of communication and multiple meetings, and repetition going through the issues. For families who are battling a relapsed cancer, unfortunately, they often do not have many other choices, and so it is a very different conversation. They have already been through an incredible amount and they usually come in knowing what they are facing and are very certain about what they want. It is the diseases that are not related to cancer where the family has really struggled with this decision and have to accept a risk that happens upfront, a small risk, but a real risk of their child dying during the transplant, we say the numbers are about 5% to 15% depending on the type of transplant, in order to provide a cure for their child. There is no easy way to help families make that decision except by giving as much information as we can, and reviewing it over and over and taking the time to make the decision. Bone marrow transplant, except for rare circumstances, is not really a rush event.

Foss Can you talk a little about the whole issue of consent, say from the children themselves? I know that in clinical trials when a child is of a certain age, they have to give not consent, but assent, to participate or they have to be aware of what they are going through. At what age do you sit down and talk to the child, him or her, about the process?

Chirnomas It depends a little bit on the child, of course, and on the family. Officially, the age for assent is somewhere between 6 and 8. Even that young we are asked to try to get assent, but certainly in children 10, 11, 12, and older, we do try to get some sort of buy-in from them that they understand they are going to be hospitalized for a long time and that they are going to be a little bit uncomfortable and have mouth sores, and we try to tell them some of it, but basically, we work with the families to try to do an age-appropriate consent, and I think the key things that we have found, are that children appreciate more information because usually their imagination is way beyond what we can ever imagine, and so often we find that the children are much happier knowing what is coming. We find that even just in general pediatrics, kids just like to know what their day is like and what the plan is, and so in the same way, preparing them as much as we can, we find to be very useful.

Foss In terms of the whole issue of clinical trials, are most children transplanted on clinical trials? What is the role for clinical trials in that setting?

Chirnomas That is a fantastic question. They should be on clinical trials. The success we have seen in 25:53 into mp3 file http://yalecancercenter.org/podcast/jun1911-cancer-answers-chirnomas.mp3
pediatric cancer, whereby we have now made leukemia, ALL, go from basically 0% chance of survival in the late 60s, early 70s, to virtually 90% survival to mid-80%, we need to approach transplant that way; however, because it is a much more rare process, we do have many clinical trials, but we do not capture every child on a transplant, and so that is kind of a moving target and something that the Pediatric Blood and Marrow Transplant Consortium in the United States is working on.

Foss Can you talk about some of the major outstanding research issues in this area?

Chirnomas I think you already mentioned one of them, which is reduced-intensity regimen. Currently we are learning that we can modulate the immune system in a way that uses medicines that are not as toxic to the rest of the body but help allow for the new bone marrow to come in, and that type of regimen, called reduced intensity, is really an area of active research and we need to understand how well it works, in what settings, and in what diseases. Other things that we need to understand better are better regimens to cure some of the more difficult leukemias that even though we can transplant them, our outcomes are not as good as we would like.

Foss What about if a child fails a transplant, if a child relapses after a transplant, say an allogeneic transplant? Is it possible to go back and transplant again?

Chirnomas It is, and we have done so, and obviously each time you go back there is the higher chance of side effects as well as probably a lower chance of cure, but there actually have been cures doing this, especially if the relapse happens fairly far apart, but we definitely do that, especially with the leukemias.

Foss If you look overall at all the diseases that are transplanted for children, you mentioned that there have been some tremendous successes, can you tell us briefly, other than leukemias, other successes in other areas?

Chirnomas Aplastic anemia is sort of the poster child of pediatric bone marrow transplant. Aplastic anemia is a process by which children acquire a virus and their bone marrow stops producing cells, and in that case, the only way to help them is to give them a new bone marrow, and when they have a sibling or a relative that is a match, they really do amazingly well. It is almost as if they do not get sick. It is a pretty incredible process, and so that has been a great disease that we have had a lot of success with.