

Yale CANCER CENTER *answers*

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Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at the Yale Cancer Center, Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about pediatric cancers and bone marrow transplant with Dr. Debbie Chirnomas. Dr. Chirnomas is Assistant Professor of Pediatrics in Hematology/Oncology and Director of the Pediatric Bone Marrow Transplant Program at Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar Debbie, let us start off by talking about pediatric cancers. When we think about kids getting cancer, it breaks everyone's heart, but not a lot of people know what kind of cancers kids get, how often they get cancer and how it is treated, so why don't you tell us a little bit more about that to set the stage.

Chirnomas The most common childhood cancer is leukemia. Within that, the most common type is ALL or acute lymphoblastic leukemia and then the second most common is acute myeloid leukemia. Second after that would be brain tumors as a general group and then after that is a variety of different solid tumors.

Chagpar How do kids present when they present with leukemia and what are their options?

Chirnomas Often they present to their pediatrician with either being pale or tired or having bruising that was unexpected. Occasionally, there can be nosebleeds or unexpected bleeding. A lot of times, they feel fine and they come for other reasons like a cold and it is picked up on routine blood work, so there is a pretty wide range of symptoms.

Chagpar I can imagine that must freak parents out, you take your kid in for what you think is a cold and the pediatrician does some blood work and then says, oh, by the way.

Chirnomas It can be very shocking. What we try to tell parents is not to be concerned about every bump, bruise, or little swollen node. Because the other thing that families get very worked up about is what are called swollen glands, which we call enlarged lymph nodes, and most of the time, probably more than 90% of the time, it is nothing. We have talked about the fact that if the symptoms persist or if your child after a week of some type of illness is not recovering and just not themselves, that is a reason to seek medical care, but then most things are not cancer.

Chagpar Thank goodness for that, but let us suppose your child does have cancer, leukemia, what happens then? How is it diagnosed and how is it treated? What are the options?

Chirnomas In the United States, we are very lucky in that we figured out a long time ago, in the late 60s or

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early 70s, that because it is such a rare disease, and I should have mentioned at the beginning that in total there are approximately 12,000 new cases of childhood cancer a year, 30% of that is leukemia, so it is a relatively small number and in order to get effective treatments, we you knew early on that we needed to be in cooperative groups, so we really were the pioneers, I would like to say, of the cooperative group treatment and with those therapies we have really come a long way from back in the 70s where the survival rate was basically 0 to by the 90s, it was in the 70 and 80% survival and now it is even a little bit higher.

- Chagpar For our audience, just clarify what you mean by cooperative groups because people might not be familiar with that term.
- Chirnomas Basically, if you go to any children's hospital across the country or pediatric tertiary care center or big hospital, almost all of us will be using the same exact treatment to treat childhood leukemia. Occasionally, we have smaller trials that are going on but they are all very similar and most of us are using what is called a Children's Oncology Group trial.
- Chagpar And I think that is really important because a lot of people say, well you are doing all of this great research but it is research going on in silos, and I think that your point is that particularly in the childhood cancers where they are so rare that you do find this cooperation amongst all of these large cancer hospitals so that you guys are working together to really find answers to pediatric cancer by doing the clinical trials that all of you can benefit from.
- Chirnomas Absolutely, it has also provided a tremendous support to the smaller centers, so if you are in a more remote area of the United States that might not have access to the key leaders in the field, it is okay because if you are part of the cooperative group, you are going to have access to those people and you are going to be able to offer that therapy to the children in your area, so it has provided a great safety net of quality of care across the board as well.
- Chagpar And I am sure that that makes a lot of parents out there just feel really relieved. Let us suppose you have the unfortunate incident of going to the pediatrician and having them find on some blood test that there is a suspicion of leukemia. What happens then, I think parents automatically start thinking, oh my God, my kid has cancer, what am I going to do? Can you kind of walk us through what the treatment is like, what is the prognosis like, should parents be breathing deeply or is this something that is really concerning?
- Chirnomas The first differentiating point is what kind of leukemia, so ALL which is the most common kind is very treatable and our cure rates now are upwards in the high 80s to low 90s which means that most children that have ALL are cured, and when I say cure, families wonder what that means, it means gone forever and not coming back. AML, acute myeloid leukemia, is a little harder to treat and the cure rates depending on the exact type can be a little bit lower, but they are still quite good, so I think what happens when families first hear the news is that like all families they have shock at any kind of scary diagnosis, but then we fairly quickly are able to follow up with them with a

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really detailed plan. For ALL, the most common kind of leukemia, it is approximately 3 years of treatment which again is daunting when you first hear that, and the first six months are very intense and involve a lot of coming back to the hospital. After that, children by and large are able to resume most of their life and school and their world can sort of carry on, so it sounds overwhelming but we give roadmaps and very clear delineated plans, and I think we have done a pretty good job of walking families through it and having them feel like they know who to call if they have questions and what to do very early on.

Chagpar So in that first six months when you talk about really intensive therapy, what are we talking about? Are we talking about chemotherapy?

Chirnomas For leukemia, the initial treatment is chemotherapy and again we use many different agents that leukemia is susceptible to, and so we found that the best cure rates are when we combine drugs, so the initial first month of therapy is quite intense, sometimes the children are in the hospital for much of that time but not always and that is a four-drug combination and then afterwards there is a flip-flopping and a complicated recipe of different agents that we again clearly outline for families and that goes to coming to the clinic a couple of times a week and we monitor things very closely for those first few months.

Chagpar Yeah.

Chirnomas And sometimes there are hospitalizations that are unexpected for fever, or other events, so we counsel families that the first few months are very overwhelming and we try to provide psychosocial support and social work support and as much resource support as we can. After that, life does start to normalize back which is hard to believe but it does happen.

Chagpar And that is great for the 80 to 90% of people who respond and a very good friend of mine, his son was diagnosed a few years ago with ALL, and got chemotherapy. This was at a time when there was a shortage of methotrexate and his son was caught in that which was really unfortunate, a drug which is standard of care and relatively cheap was something that really makes a difference to kids with leukemia and that was problematic, but in any event, he was doing fine and I ran into my friend just a couple of weeks ago and asked how his son was doing, and he told me that he had relapsed and was now looking at having his spleen out and a bone marrow transplant. How does that happen?

Chirnomas Well during the first few years of therapy, as I mentioned, the first three years, we do monitor closely, and as you mentioned, there is a small percentage of kids that will not respond as well, or the therapy will not cure the leukemia and so we see that come back usually on the blood work. Sometimes, the families come in and say, he is acting just the way he did at the beginning, I am really worried and a lot of times, they are right. We trust parents' intuition, and so when that happens, the good news is we do have a second line therapy that is very effective, which is called

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a bone marrow transplant or hematopoietic stem cell transplant where we take the stem cells in the bone marrow that are used to make your immune system and your blood cells and your platelets, and we give them from another person to the person with leukemia and that actually provides a mechanism of fighting the cancer. The stem cells from other people can actually help fight the cancer. In addition, we combine that with a much stronger chemotherapy regimen which sometimes includes irradiation and sometimes does not and so we put them through this process which is quite lengthy and we do have very reasonable cure rates, not as good as the initial chemotherapy, but depending on the match and depending on the type of leukemia, it is very promising for some children.

Chagpar When we talk about transplant and we talk about taking somebody's liver and transplanting it into somebody else or somebody's kidney, people talk about rejection, and the fact that your body and your immune system does not particularly like stuff that is foreign to it. Does the same thing apply in bone marrow transplant?

Chirnomas Absolutely, and we talked about the fact that we are trying to match two immune systems, so unlike a liver or a kidney where we can give a little bit of medicine to keep the immune system from rejecting the organ, in bone marrow transplant, we actually take away the immune system altogether in order to allow the new immune system to start to work because part of what we are transplanting is the immune system itself and there is good and bad to that, so the good is that we can start with sort of a clean slate and that means that when it works well the children or the grown-ups do not have to stay on the medicine to suppress their immune system for life. They actually come to accept that new immune system as their own, so they are not on lifelong medicine when it works well. The bad side is that when it does not work well, you have a recipe for either the new immune system to attack the person's body, and that is called graft-versus-host disease or the reverse which is less common where the old immune system has a little fight left in it and it says, get out of here, this is not your turf and we do not call it graft rejection, we call it graft failure, but either situation can be life threatening.

Chagpar We are going to talk a lot more about bone marrow transplant and how kids with leukemia get through it right after we take a short break for a medical minute. Please stay tuned to learn more information about pediatric cancers with my guest Dr. Debbie Chirnomas.

*Medical
Minute*

The American Cancer Society estimates that in 2014 over 1500 people will be diagnosed with colorectal cancer in Connecticut and nearly 150,000 nationwide. When detected early, colorectal cancer is easily treated and highly curable and as a result, it is recommended that men and women over the age of 50 have regular colonoscopies to screen for the disease. Patients with colorectal cancer have more hope than ever before due to increased access to advanced therapies and specialized care. Clinical trials are currently underway at federally designated comprehensive cancer centers, like the one at Yale and at Smilow Cancer Hospital to test innovative new treatments for colorectal cancer. Tumor gene analysis has helped to improve management of the

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disease by identifying the patients most likely to benefit from chemotherapy and newer targeted agents resulting in more patient specific treatments. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to the WNPR, Connecticut's public media source for news and ideas.

- Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Debbie Chirnomas. We are talking about pediatric cancers, and particularly leukemia, and right before the break, we were talking about bone marrow transplant. For those of you who were with us before the break, I was telling the story of a very dear friend of mine and his son who was diagnosed with leukemia who is now facing a bone marrow transplant and Debbie was starting to tell us about how essentially if I have got this right Debbie, you are taking away the kids immune system and giving them a new immune system and hoping that their new immune system kind of gears up and fights off this cancer rather than their old immune system fighting the new one.
- Chirnomas Yeah it is a combination approach, so we give very strong chemotherapy and/or total body irradiation and if we did that alone without doing anything else, we might make the leukemia go away for good, but we also would destroy in the process the person's natural bone marrow, innate bone marrow, and that would leave them without the ability to make their own blood, so it would be damaging good cells as well as bad, so we have to rescue them with something. It turns out that by rescuing them with bone marrow from someone else it gives this added advantage of the new immune system seeing the leukemia as foreign and providing benefit on that side as well, so it is a double approach or a dual therapy approach. It is called graft-versus-leukemia. The new bone marrow is called the graft, kind of like a kidney or liver transplant and that effect has been more pronounced in acute myeloid leukemia but has also been seen with acute lymphoid leukemia and also even some lymphoma, and we are doing more and more research to hone in on that and try to obviously then hopefully someday take advantage of it more specifically.
- Chagpar Where do kids get this marrow, do they get it from their parents, from a sibling, can anybody donate? Is there enough bone marrow out there or are you suffering from a shortage just like we are suffering from a shortage of organs?
- Chirnomas I am glad you asked, that is a great question, so unlike with solid organs, we do not suffer from a shortage in terms of the renewability. Kind of like a palm tree or something, it is a renewable source, bone marrow, so if you donate bone marrow to someone else, your body will make more which is an amazing thing. Where we get into trouble though is when we do not have someone who is an immune match, so unlike solid organs, we need a closer immune match because even though we are replacing the immune system, we are not perfect at getting rid of the original immune system and so the new immune system, the more similar it can be to our own immune system, the less likely there will be a war waged one way or the other, either the new immune system attacking the person or it getting kicked out and being rejected. So that process is called

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HLA typing is a very important process and that is where we get hung up. So while we have plenty of bone marrow in theory, we do not have the right matches always. There is an incredible organization called the National Marrow Donor Program which you can go to at marrow.org that was started by a family who had one of the first children to have a bone marrow transplant in the United States and it turned out that the donor for their child was a lab tech in one of the research labs in Seattle in the lab of Dr. E. Donnall Thomas, who won the Nobel Prize for bone marrow transplant and the technician happened to randomly match this young child and the family saw the power of unrelated donor options, and so they started this organization. In general, we do look for family donors first, so we check mostly siblings, who are the most likely to match, full siblings, half siblings generally do not match unfortunately and very rarely in a small percentage of cases, parents can match fully, so we do look to the family first but then we go to the general public. Only 30% of families have a match, maybe even less depending on the cultural population. There are 15 million donors in the registry and it is growing all the time. I think the limitation is that we find that there are certain minorities not represented, so the black population is under represented. The Hispanic population was under represented but has actually had a big surge in drives and is actually a little bit better these days, but it is just a cheek swab, so if you come across a bone marrow drive, it is really very little effort to go and join and so we always encourage everyone to sign up. You can always say no later on.

Chagpar But you could probably save a kid's life.

Chirnomas Yeah, it is a procedure. It is not giving up a kidney or liver, but it does require both medicine and some IV intervention wherein your blood goes on a machine or a minor procedure in the operating room where we put needles into your back side while you are totally asleep, and we remove some bone marrow. For children, it is usually a small amount. That is the preferred method for children. We know that it results in less graft-versus-host disease if we use the bone marrow directly, but people that I know that have donated have said it is the most incredible experience they have had and eventually, after about a year or two years, depending on the country, you are allowed to communicate, the donor and recipient are allowed to communicate.

Chagpar It is mind boggling to me because I cannot imagine being a parent who is not a match and having your child with leukemia that has relapsed and struggling to find a donor and if only 30% of families actually have a donor within them, this is a good reason to be nice to your siblings.

Chirnomas Exactly.

Chagpar You are really counting on the generosity of your fellow citizens, so it is really important, and incredibly rewarding, I can imagine, but let us get back to the patient. Let's suppose that the child actually does have a match and is going to get this bone marrow transplant, when you talk about this high-dose chemotherapy and potentially whole body radiation, I am thinking that that is an incredible insult to this poor child's body. What is that like? What do they go through?

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Chirnomas It is about a four-to six-week hospitalization where they come into the hospital in as good a shape as we can get them, and we try to let kids get as healthy as they can be from their prior therapy. Then they come in and they get a few days of whatever the combination is, it is usually about a week of therapy in the hospital with a special IV put in or they may already have one, but we sometimes have to put in another one called a central venous line and then we give them the new bone marrow and that part is the easy part, so, unlike surgery for other organs, this really just looks like a blood transfusion. It is very uneventful, the actual transplant, and then we wait, and we wait for the bone marrow to hone inside the long bones and start working. It is actually an incredible concept that this blood gets put into the peripheral blood, your regular blood stream, and it knows where to go instead of getting flushed out somewhere, it just hones in on the right place. I think that is one of the miracles of the whole thing and it sets up shop, and after about three to four weeks after it is given, it starts to produce white blood cells, those are the first cells, so it starts to make the immune system cells right away. After that time, it then starts to make the other blood cells as well. During that time though other cells, as you pointed out, it really is an insult to their whole body and healthy cells are damaged as well, and so the children get mouth sores and sometimes very significant mouth sores from their mouth all the way down to their bottom.

Chagpar Wow.

Chirnomas So they are often very nauseated and in a lot of pain. We are very aggressive, both in adults and pediatrics, we are very aggressive about pain management and children are often on an IV pain drip that they can control if they are old enough or otherwise that we manage for them. There are a number of other medications to help control the nausea and we give them nutrition as they go through this process. What is incredible is that they also can lose their hair and sort of 'normal' things that you might get from chemotherapy. There are a number of other risks. They can get serious infections, they are kept isolated in this room in general. Some facilities have wards that are totally walled off and so they can walk in a ward, but at most places they are in the room for six weeks. So it is a long hospitalization. What is amazing is that when the white cells start to be produced, it is like this miraculous recovery, so you have been doing all this stuff to try to keep them safe for weeks and then all of a sudden, their mouth is healing right in front of your eyes and all of a sudden they are smiling again and they say, can I have a drink? I mean it is not quite that dramatic for every child, but often it is, and it is really amazing. Parents do not believe us that it is going to happen when they are in the middle of it and we keep telling them, no it is going to happen, and so the process of recovery can go very well. Children are very resilient and they are inspiring in the way they heal and are ready to play as soon as they have the opportunity. Once they go home, they are in an immunocompromised state for a number of months, and so they feel better but they are bored out of their minds, and often that can be almost the hardest part to be housebound and bored, but we like that part.

Chagpar When you say that they are isolated and housebound, that means no school, no friends, no play, no sports, no nothing?

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Chirnomas Well, outdoors is okay, and if you think about it, it is all about infection control, so outdoors with great airflow is great, so anything outdoors, maybe not a football game, but anything without massive crowds is okay, but otherwise, yeah, no friends, no school, no malls, no church, no movie theaters, it is no stores, no takeout food, because as you might imagine, the bacteria that we find in food from restaurants is a big no-no, so we find in our adolescent and young adult patients that this is really the hardest part. They can handle a five night hospitalization but when it comes to asking them to sit at home for sometimes upwards of a year when they are feeling actually pretty good is incredibly challenging and it is very difficult to their self-esteem and to the sense of who they are. They are either young college students or high school students and often strangely that psychosocially ends up being one of the more challenging parts to get them to comply with and keep taking their medicines to protect them.

Chagpar Debbie, I am going to play the devil's advocate and try and channel my inner young adult. If I was an adolescent who was just told, you need to stay home, no friends, no school, no malls, I would say, wait a second, so my parents are allowed to be in the same house as me, my siblings are allowed to be in the same house as me, what is an extra one or two or six or 10 other people? I mean what about my boyfriend, what about my best friend, and what about my best friend's best friend?

Chirnomas We do struggle with this, and we basically take it on a case by case basis. We set up the strictest rules to start with and then depending on the bent of the given person, some kids, you would be amazed, they do not want anyone near them because they are freaked out, or they just want this to work, but many more, as you say, want x number of people to be allowed. If there is a boyfriend or girlfriend, first of all, you are not really allowed to have intercourse and that is challenging for teenagers sometimes. Parents are usually happy, but we basically do it case by case. We explain to families that we can only give the advice and that they need to follow what they feel is best for their children and what they can get their children to do. A lot of times it is about handwashing, screening people for illness when they come over. In the adults, well they are much more flexible and as we move forward, we really need to find that common ground for young adults; if it means they are not complying, then we have to meet them in the middle, and so we are constantly trying to do that.

Dr. Debbie Chirnomas is Assistant Professor of Pediatrics in Hematology/Oncology and Director of the Pediatric Bone Marrow Transplant Program at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another addition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.