



Pediatric Oncology

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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 pediatric oncology with Dr. Gary Kupfer. Dr. Kupfer is Professor and Section Chief in Hematology and Oncology at Yale School of Medicine and the Clinical Program Leader at Smilow Cancer Hospital. Dr. Chagpar is an Associate Professor of Surgery and the Assistant Director for Global Oncology at Yale Comprehensive Cancer Center.

Chagpar Gary, let's talk about childhood cancers. When we think about kids with cancer, first of all, I think that the majority of us think that this is very rare and also very tragic. Can you give us a landscape of what pediatric oncology looks like?

Kupfer You are right that it is a rare cancer compared to the general population, but I like to tell people that the diagnosis of cancer in children really touches everybody. All one has to do is calculate the effect on siblings, parents, extended family, friends, neighbors, schoolmates. You begin to add all that up and realize that the effects are really far ranging.

Chagpar Not only that, but you talk about the years of life that children with cancer have as a potential future and that is significant.

Kupfer There is no doubt about that, and when one wants to be completely thinking in objective terms, one can actually calculate it, and there are people in our field who do that, the effect of such a diagnosis on the long term, in terms of being a productive, tax-paying member of our society, and it can also be calculated in terms of the long-range effects after having undergone treatment for childhood cancer. In economic terms, those effects could really be quite impactful as well.

Chagpar How many kids in general in the United States, for example, are diagnosed with a pediatric malignancy every year? Just to give our listeners some kind of framework of how many people we are talking about.

Kupfer That can be calculated in a number of ways. If you calculate it in terms of patients all the way up to even 20 to 25 or 30 years of age, that can be 25,000 to 30,000 people. Sometimes, the numbers get reported in a much tighter way up until the age of 15 where the numbers perhaps are only 10-15,000. Either way, you can understand how the numbers are really quite wide ranging all the way from diagnosing a patient at

3:42 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-1021-Podcast-Kupfer_344742_5_v1.mp3

newborn age, all the way up to 25-30 years of age. That is a really broad range of age when one considers developmentally where a patient might be, not to mention the effect where the patient is at that time of life, whether one is in school or working.

Chagpar When we talk about pediatric oncology, it really is such a heterogeneous bucket of diagnoses. When we talk about adult malignancies, even when we talk about breast cancer or lung cancer, we say all breast cancers are not one thing and all lung cancers are not one thing and all colon cancers are not one thing, and when we talk about pediatric oncology, that really includes a whole myriad of diagnoses. Can you tell us a little bit more about what are the most common malignancies diagnosed in children?

Kupfer Well, your point of being quite heterogeneous is really, really true. In terms of total numbers, the most common type of cancer in children would be leukemia. And even within that bucket of diagnoses, that really encompasses children from newborns who can present with leukemia, all the way up to young adults. And that type of cancer, leukemia per se, looks very, very different in those 2 extreme age ranges. And indeed, the treatment is equally extreme. So, the approach really has to be quite different in terms of cold-hard therapy terms. Treatment is actually quite different as well in terms of approach from the care itself. One obviously has to approach a young child very differently than the way one manages the young adult. That is really both the challenge as well as the wonderful nature of being a pediatric oncologist.

Chagpar But I can imagine that there is also heartache associated with being a pediatric oncologist when you are surrounded by kids every day who are diagnosed with cancer and potentially lethal cancers. How lethal are pediatric cancers in general?

Kupfer I would say that pediatric oncology really represents a miracle in consideration of modern medicine. If one goes back before 1948 where in our field the age of modern chemotherapy began, the survival rate for a child with leukemia was in fact 0. Nowadays, the survival rate for a child with leukemia is approaching 90%. It is really quite an amazing turnaround. That is not to say there are not amazing incredible challenges that remain in the treatment of childhood cancer even in leukemia, and there are specific cases of cancer which really are quite difficult to manage and deal with and still challenges all the way to getting a cure.

Chagpar Let's talk a little bit about childhood leukemia, since it is the leading malignancy affecting children. You mentioned that it can affect the spectrum of children from newborns all the way up to young adults. How is the presentation of leukemia in those 2 extremes different and how is your approach different? You mentioned that the treatments are different as well.

7:06 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-1021-Podcast-Kupfer_344742_5_v1.mp3

Kupfer As one can imagine, when you are trained to figure out what is going on in a child who might have leukemia who is perhaps let us say 3 years old, which is the most common age for presentation of childhood leukemia, the symptoms of childhood leukemia might be pain, might be fever, might be bruising, might be paleness, and you can imagine those symptoms really do not hone in on identifying a diagnosis at the snap of a finger. Not to mention the fact that the average 3-year-old who is not feeling him or herself is not going to pull the chair up close to you in the examination room and go through a dialogue with you. So, that is not only the challenge of oncology that is also the challenge of pediatrics. On the other hand, even in a young adult or adolescent who has leukemia, all of those symptoms may present and you still might not really understand what is going on until you start probing a little more, and in fact, often with a little bit of time and some selective blood tests, things become more in the focus at that point, but even at any age, the signs and symptoms that come about with leukemia really can be quite difficult to nail down and it can often take weeks before the diagnosis comes to the forefront.

Chagpar I am sure that some of the parents who are listening to our show today may have an average 3-year-old infant who may have pain, may not be acting themselves, may look a little pale, should they be worried? When should those symptoms trigger a visit to you, the doctor, and what happens for you in the clinic to actually nail down that diagnosis because I can imagine that that is really a difficult task?

Kupfer Absolutely. I think the key is number 1, for everybody to have a trusted and regular pediatrician in your life. One has to establish that relationship from day 1 with your child. Then, overtime, that pediatrician who gets to know you and your child can understand progression from first encounter of symptoms that you might report to the pediatrician to then over the course of days or even a week or two that the pediatrician then starts to become more and more suspicious, more and more concerned that will then trigger a more full workup. And indeed, for most cases of leukemia that I have encountered, the diagnosis never comes about within one snap of the finger and there is a tincture of time that indeed is required to fully and better understand what is going on. I really always try to send the message to the parents that there is nothing they could have done differently, almost never, and in fact, one having diagnosed leukemia a week or two ahead of time versus today, almost never has any impact on the eventual outcome because one has to remember that leukemia is really a head-to-toe disease. This is not similar to breast cancer or prostate cancer where early detection and identification at a very early stage really makes as big a difference.

Chagpar Let's say a parent brings a child to the pediatrician and over a week or two, the pediatrician starts to get suspicious that this child really is not the way that they

normally are and that something is going on, tell us more about what the workup involves, how do you get that diagnosis?

Kupfer The very first and basic part of any evaluation is a good history and a good physical exam. As I mentioned, some of the historical symptoms that one might gather tend to be a bit nonspecific as we say, which is why a physical exam may actually be more important in diagnosing a child with leukemia. We might find enlarged lymph nodes, we might find a big liver, a big spleen, we might see paleness, we might see bruising, all of which are really going to trigger a very obvious laboratory workup. That workup is going to entail getting a blood count in which we might start to get some indication that there is something deeper brewing, such as low red cell count, low white blood cells or high white blood cell count and a low platelet count, all of which will culminate in the diagnostic examination of the bone marrow. So, the bone marrow is of course the blood factory of the body and that is where all of the blood cells are made. And in fact, that is where one is going to see the eventual effects of leukemia. Leukemia as we all know is the uncontrolled growth of normal blood cells that convert into cancerous blood cells, and by doing so, those blood cells are going to crowd out all the normal blood making machinery in the bone marrow. So, by going to the heart of the matter, which is really the bone marrow, that is where we begin to identify exactly what is going on.

Chagpar A bone marrow biopsy sounds like a painful procedure, is that done as an outpatient or is that in an operating room for children who are say 3 years old?

Kupfer Actually we can do it in a number of different ways. We can do it outpatient, we may actually do it in the operating room if a child is going for anesthesia for some other reason. There are a number of different ways that we will actually try to find an opportunity, take advantage of anesthesia. One way or the other though, we do use anesthesia in children. That might be a little sedation given through an IV. It might again be taking advantage of general anesthesia if that child is there for some other purpose in the operating room. Either way, we use a rather large needle to go and get a little sample of bone marrow, usually in the pelvis bone. As I mention to family's or anyone else whom I am about to undertake a bone marrow examination, it is truly a very easy procedure if you are listening, you can feel the back of your hip, you can feel your pelvis bone actually protruding and that is exactly where we normally go to get bone marrow, and it is so near the skin that it is an absolutely safe procedure. It can be a little painful, which is why we do go to great lengths to lessen the pain with a variety of different pain medications.

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Chagpar This has just been fascinating learning about bone marrow biopsies, and I want to learn more about how we actually treat these children with childhood leukemias and other childhood malignancies right after we take a short break for a medical minute. Please stay tuned to learn more information about pediatric oncology with my guest, Dr. Gary Kupfer.

Medical Minute

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This is a medical minute about breast cancer, the most common cancer in women. In Connecticut alone, approximately 3000 women will be diagnosed with breast cancer this year, but thanks to earlier detection, noninvasive treatments and novel therapies, there are more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer. Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety many women experience. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.

Chagpar This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Gary Kupfer. We were talking about pediatric oncology and right before the break, Gary was telling us that the number one childhood malignancy that is diagnosed in the United States is leukemia and that the average age of these patients is 3 years old, they present with nonspecific symptoms, kind of feeling not themselves, a little bit of pain, they might be a little bit lethargic, they might be a little bit tired, they might bruise a little bit easy, they might be pale and that really having a good pediatrician who can do a physical exam and start the workup of these patients is critical. And that workup includes a blood count and ultimately a bone marrow biopsy, which is the part that we got to right before the break. Gary, you have a child and they have gone for this bone biopsy, which you were telling us is not an extraordinarily difficult procedure, it is fairly simple and is done with anesthetics, so that these children are not in pain. If a diagnosis of leukemia is rendered at that point, what does treatment look like? I mean you were saying that pediatric oncology is kind of a miracle in the sense that now we are getting survival rates up to 90% with these children, what does that treatment look like, how easy is it for these kids to go through this treatment?

16:41 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-1021-Podcast-Kupfer_344742_5_v1.mp3

Kupfer Well, in particular for leukemia, this can really entail quite a commitment to a long, long road of chemotherapy. In general, 2-3 years' worth of chemotherapy. So, it is quite a commitment for families. The first 9 months or so of leukemia therapy is actually quite intense with the first part of it being given in the hospital. And overtime, once patients come out the other end of that relatively intense period of chemotherapy, they really do actually kind of get into a rhythm of therapy, which entails coming into clinic, getting chemotherapy there but also taking oral chemotherapy at home. Either way, it is a long road and inevitably there are going to be some bumps in the road with side effects from therapy. But the wonderful thing is families kind of get into a rhythm of sorts of coming to clinic, going home, carrying on with their lives because let us face it, 2-3 years is a big, big commitment and families and parents and jobs cannot be put up on the shelf, they have to kind of continue what they are doing, they have to maintain their health insurance, they have to see to the other children. And the impact on the rest of the family is quite significant. So, they have to carry forward. Now, there are some varieties of leukemia that actually have to be treated straight away with bone marrow transplant. So, even when we get a bone marrow test done, committing a patient to a particular road, there is actually a fair amount of workup that continues for the initial couple of weeks, which then points the road to which direction things are going to go.

Chagpar You can imagine people that may have gone through chemotherapy, it is often quite rigorous, but especially for children, in those developmental years, with the average of 3 years old and this is a 2- to 3-year course of therapy of chemotherapy for some of these kids, how does that impact their early childhood education and going to kindergarten and starting school and all of those things that kids should be doing at that time?

Kupfer Well, as you could imagine, it is really, really complicated; to the greatest extent possible, we want not only the families and siblings but the patients themselves to carry on with their normal lives. For most of our patients, they are able to do that. They are able to go back to school. They are able to carry on and they are able to live a normal life. But there is no doubt that the patients who have relatively intensive chemotherapy for example, and by the way, I should just say that depending on the biology of their particular leukemia, depending on some of the workup that we identify from a biologic point of view can actually dictate a relatively less intense chemotherapy course or a more intense chemotherapy course, and as you can imagine, those who undergo relatively more intensive therapy can have more side effects, which takes the shape of a more chronic illness type of situation, patients who perhaps miss more school who perhaps do have some neurocognitive effects from the therapy itself. So, for types of leukemias and cancers that require more intensive intervention, there

indeed can be a price that is paid in terms of outcomes and that can be from a head-to-toe point of view. These kids can have a side effect in every organ system itself, and as a result require extraordinary amounts of potential intervention as they go through life that really reflects every organ system as I mentioned, as you can also imagine neurocognitive effects really manifest themselves greatly when it comes to school and beyond that, university and jobs.

Chagpar Yeah, I was going to ask about that because we have all heard about chemo brain and when chemo brain occurs in kids at such a young age, what are the long-term effects of that? I mean, do we see that there is a clear difference between children who have been treated with chemotherapy for leukemia at a young age and control patients when you look at down the road, their cognitive performance on university entrance exams or school work or other things?

Kupfer Well, that clearly affects neurocognitively and that can be manifested in something as cliché as an IQ or even college entrance exam, but a lot of those sorts of outcomes are complicated a bit because mental health is affected, and as we all know, it is very hard to separate out the effects on mental health as well as neurocognitive effects. So, it can be very tricky. We do just simply know that all of these things can be affected by having undergone therapy for again a whole variety of different cancers, and we are really not just talking about chemotherapy, especially in the realm of brain tumors, which take up a very significant fraction of pediatric oncology, upwards of 25%. Radiation therapy is a very mainstream modality for those patients, and one can imagine that radiating the developing brain can have a great deal of effect. So, it is very complicated and often almost impossible to identify one specific factor as predominating when it comes to treatment of these kids. It can really be multifactorial and indeed the overriding effect of having to deal with a chronic illness, having to deal with a life-threatening cancer and how does that affect someone going forward not only while you are in the midst of treatment but also having to deal with the potential for recurrence, something that the patients but perhaps more of course the parents have to deal with – when is that other shoe is going to drop when a patient has to encounter recurrence.

Chagpar Are there support groups for families who have children with leukemias and are going through these? Because I can imagine that is a harrowing experience and you probably may be very confused as to what to do and scared about what is going to happen next, and I can just imagine what that would feel like.

Kupfer One thing that we have really focused very much on is not only the medicines or the supportive care for these patients but in developing the psychosocial support system for patients. In our clinic, we really work hard to provide a whole range of supportive

24:10 into mp3 file https://cdn1.medicine.yale.edu/cancer/2018-YCA-1021-Podcast-Kupfer_344742_5_v1.mp3

care including social work, psychology and psychiatric services. In my mind, those are as important as the chemotherapy we hang upon the IV pole, and in doing that, we really do try to provide comprehensive care for families, and again, not just for the patients but the siblings and the parents. Siblings probably have more mental health issues than those patients going through the therapy themselves.

Chagpar Why is that, is that just because of the bond between siblings and watching your sibling go through something or is there something more to that?

Kupfer No, I think when you are the healthy child in the family, number 1 – you may be anticipating for that to perhaps happen to you. You may be acutely aware that the attention is focused on another child. As I mentioned to you, that can often be up to 3 years of therapy and it could go on if recurrence occurs. And often, the sibling can feel shunted aside unfortunately, but it is perfectly justifiable the focus of parents has to be on the child who is currently going through therapy. So, there are incredible ramifications for the whole family. This is something that really has reverberations all through those lives at the child who is going through himself or herself this diagnosis and therapy feels, it is more than that.

Chagpar The other question that I have is, on this show we often talk about clinical trials and we talk about how participating in clinical trials really helps to move the field forward, whether we are talking about breast cancer or colon cancer, prostate cancer or whatever; in pediatric cancers, I can imagine that research takes a whole different flavor because patients are young and they may not be able to understand clinical trials. Tell me more about clinical trials and clinical research in pediatric oncology.

Kupfer Well, the medical miracle I talked to you about earlier that has happened in pediatric oncology to go from 0 to 90% cure rate in leukemia, all of that work initially happened in pediatrics. So, there is a really rich and long tradition of clinical research and clinical trials work in pediatrics. But because of the small numbers that we have in pediatrics relative to our adult colleagues, it really requires the collaboration of centers all around the country and that is indeed what we do in a central organization called Children's Oncology Group. So, we have a whole range of protocols as we call them for clinical trials for patients with a whole variety of different childhood cancers. In addition, on our own, we are trying to develop a new and experimental therapy for children with very difficult-to-treat cancers and some of those are actually developed in concert with our collaborators here at Yale, and very often some of those trials have to be follow up trials after the adults have undergone them to indicate what may be the right applications for some of those new and experimental drugs.

- Chagpar So, clinical trials are still available for kids, and parents who have children who are faced with a malignancy should ask their oncologist about clinical trials because potentially they can benefit and benefit future children, is that right?
- Kupfer I think it is really important because number 1 of course as I mentioned before, everything that goes on in pediatric oncology care today is based on what has gone on in the field for the last about 75 years. So, it is really important for us to keep learning, keep pushing the envelope because we certainly do not cure 100% of our patients currently. We have to keep trying to do better. And I think that it is also important to note that patients do better when they are on clinical trials, their care is better, and I am talking broadly of course, but their care is better, and it has even been shown in experimental terms and published in medical literature that people who are in clinical trials actually have better outcomes. So, I think those are very important things for parents to note when they think that being asked to be on a clinical trial somehow makes them feel like they are acting as guinea pigs, nothing really could be further from the truth.
- Chagpar Right, and in our last minute, I just wanted to give you a quick opportunity to tell us a little bit about some of the research that you are doing.
- Kupfer Well, as a clinician, I am also a scientist and I have a laboratory and the interesting thing is I work on a rare genetic disease that actually helps us understand how DNA is repaired. DNA of course is a target of almost every chemotherapy, and the fascinating thing about it is that the research I do actually ends up having important implications for the biology of not only pediatric but also adult cancers as well.

Dr. Gary Kupfer is a Professor and Section Chief in Hematology and Oncology at Yale School of Medicine and the Clinical Program Leader at Smilow Cancer Hospital. 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.