

Yale CANCER
CENTER
answers

WNPR Connecticut Public Radio



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Children with Cancer

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Yale Cancer Center Answers

is a weekly broadcast on

WNPR Connecticut Public Radio

Sunday Evenings at 6:00 PM

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Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and he is an internationally recognized expert on colorectal cancer. Dr. Foss is a Professor of Medical Oncology and Dermatology and she is an expert in the treatment of 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 1888-234-4YCC. This evening, Ed and Francine welcome Dr. Gary Kupfer. Dr. Kupfer is the Director of the Yale Cancer Center Pediatric Oncology Program and he is an Associated Professor of Pediatric Oncology.

Chu Gary, why don't we start off by defining for our listeners out there what pediatric oncology is?

Kupfer Pediatric oncology is taking care of kids and also young adults with a unique collection of cancers that show up only in children and young adults. In fact, we take care of patients who have these kinds of diseases that can show up in patients up to the age of 30 years old. They are uniquely present in children so much so that they require sort of a pediatric perspective, one which requires a unique set of treatments as well.

Foss Do all pediatric oncologists start out as pediatricians?

Kupfer Yes, we go through the same training as pediatricians and then go on to get more specialized training in pediatric cancer and blood disease.

Chu Maybe define for us a little better the age group of the kids that you take care of?

Kupfer Strictly speaking, we will take care of any patient under the age of 21. The actual peak of children getting cancer occurs in the first decade of life, usually around the age of 3 to 5, but we will get calls about patients even older who may have unique pediatric type of cancers, because they think pediatric oncologists have a unique perspective on those types of cancers, even in the older patient.

Foss How many children are diagnosed with cancer each year in the United States?

Kupfer About 15 to 20 thousand patients are diagnosed in the pediatric age range per year, which of course sounds like a small number compared to the large number diagnosed in adulthood, but of course, part of the unique aspect of pediatric oncology is the mere fact of whole families getting affected by the diagnosis of cancer within the family, parents, siblings, relatives, neighbors, and friends.

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- Chu Another big difference between taking care of young children, adults with cancer, and older adults, the area of adult medical oncology where Dr. Foss and I are, is that by in large, kids who are diagnosed with cancer actually do very well and the large majority, in fact, are cured.
- Kupfer When you compare it to other major medical advances over the last 100 years, it ranks right up there with a medical miracle. When you go back to the 1940s, zero percent of children with leukemia survived, now we are at a point in time where about 85% of the most common childhood leukemia's survive their cancer. It's an amazing turn around in terms of the outcome for children.
- Foss Isn't it also true that the first disease that was cured with chemotherapy was a pediatric leukemia?
- Kupfer That's right. The most common childhood cancer is acute lymphoblastic leukemia, better known as ALL by the medical community, and it was the first cancer which was effectively cured by chemotherapy, going back to 1948.
- Chu Whenever we think of the word cancer, the diagnosis of cancer, we obviously think of it as being very serious. In the pediatric world it is not a death sentence, and there is much to hope for right?
- Kupfer Absolutely. Taking ALL as an example, a great majority of our patients are cured. On the other hand, we still have a great number of challenges in numerous areas of common pediatric cancers, brain tumors being one of them, where not only do we have a lot of distance to go in terms of curing those patients, but we also have great challenges in dealing with the aftermath of our therapy; that is dealing with the late effects of our therapy. Patients have to deal with all the side effects for many years after going through treatment.
- Foss We have talked a lot about survivorship on this program, are there specific survivorship programs now for children?
- Kupfer There is a great emphasis on survivorship, especially in the categories of pediatric cancers where we have achieved our greatest success. ALL as I mentioned, and Wilms tumor being another one, are actually two major categories of pediatric cancer where we have gone further to try to figure out how we can peel back therapy in order to avoid long-term problems down the road. There is a great deal of progress that has been made, and shortening therapy and reducing the amount of drugs being used in an effort to avoid long

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term problems. Within the specialty of pediatric oncology, there is also a subspecialty of survivorship focusing on these long-term issues. A good sample of that is the HERO'S Clinic here at Yale in our section of pediatric oncology, which focuses on a comprehensive approach to cancer survivorship in the pediatric population.

Chu Gary, why we are on the topic of cancer survivorship, can you take us through some of the consequences of the long term consequences and complications of cancer therapy?

Kupfer When you think about a developing child, let us say in the typical age range of ALL, the common leukemia we deal with, you are talking about a child before the age of 10 that is exposed to multiple agents of chemotherapy, and potentially radiation therapy. You can expect that child, of course, to live another 50 to 70 years potentially, and is still going through development. You have to take a head-to-toe comprehensive approach, and when I say head-to-toe, I really mean it. These are children who can be affected in a myriad of ways with neurocognitive development, heart, lung, endocrine, fertility issues, and school performance. These are patients who require attention to every detail of their growth and development, and well being.

Foss Can you tell us a little bit about how children present with cancer? Ed and I are used to having patients come in themselves presenting with a symptom, and I imagine with children, often times, the diagnosis comes through the pediatrician or even a parent who notices something.

Kupfer Frankly, this goes back to what I think is a great challenge and the appeal of being a pediatrician. We have to figure out a way to make a connection with not only the parent, but also with the child, and of course a child who is 3 years old isn't necessarily going to speak up and tell you how he feels. One has to use powers of observation and interaction, and of course a lot of that starts with being a pediatrician to begin with, and of course as you mentioned, we get referrals from pediatricians, but often times some of the referrals come with very vague notions of what's going on. Maybe the kid has not been eating very well for the past months, maybe having intermittent fevers, or a little achy, hasn't been as energetic. Unless there is something discrete that you can identify like an enlarged lymph node, very often the signs and symptoms are going to be very vague and hard to put your finger on. So often the referrals that we get, the vast majority in fact, are simply those that reassure the families, reassure the pediatrician that the child is going to be okay.

Chu You mentioned enlarged lymph nodes, and obviously in young kids that have sore throats and colds all the time, they always have these enlarged glands. Truth be told, about a year ago, at the time he was 3 years old, little Josh developed a whole series of lymph nodes in his

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neck, and so you can imagine with his mom and dad both being cancer specialists, we both got very frightened and called up the pediatrician and said, you need to see and examine him because we are concerned, something is wrong. Is there something that you can do to kind of help calm down the mom and dad out there?

Kupfer As I mentioned, the vast majority of referrals we get are from outside pediatricians, referring pediatricians, really just to reassure people. As you mentioned, lymph nodes that we can feel, and parents can even feel, turn out to be absolutely nothing to worry about, it is absolutely normal for lymph nodes to react and to enlarge in response to having viral infections and colds and overtime they tend to shrink a bit, but the fact is a lot of people get worried about lymph nodes because its very easy to feel lymph nodes on a small child. In fact, as I mentioned, lymph nodes don't really shrink away, but it's more that the child grows to the extent that you can't really feel those lymph nodes any more.

Foss The other symptom that we hear about with presentation, particularly of leukemia, are children coming in with fevers. How often, just to reassure parents out there, do you actually make a diagnosis of leukemia in a child who comes in presenting with persistent fevers?

Kupfer Certainly very infrequently, very rarely do we find that because usually the next step is going to be taking a look at a blood count, and usually with the blood count one can allay the fears of those parents. Just thinking about it as a parent, children are getting fevers, especially with flu and cold season, with the great frequency, so often with a screening lab test in the pediatrician's office we can allay their fears right away.

Foss Another question Gary, as you talk about pediatric cancers being different than adult cancers, and we do share a lot of cancers like leukemias and lymphomas in both adults and children, can you talk a little bit about how they are different in children?

Kupfer What you see in children is a constellation of leukemias that may be similar under the microscope, but certainly behave differently biologically when you try to treat that patient. For instance, if you give a 3-year-old who has ALL leukemia, which certainly shows up in adulthood as well, a specific type of chemotherapy, that child, as a 3-year-old for example, with a standard ALL case, will have about an 80% chance of long term survival; that number is vastly different in adults. For adult patients with the same looking disease under the microscope, they will do more poorly. So, even though these diseases may look alike under the microscope, there is clearly a difference between an adult and a child. The other aspect of course is that children will tolerate these treatment regimens far better then the adult population will, and so on one hand, we are able to deliver a greater degree and more

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effective chemotherapy to children. On the other hand, there is a greater price to be paid in a longer run because of the reasons we have mentioned before; children have to continue to go through growth and development up and beyond the age of 21, and as a result they have to pay a price in terms of the effects of the therapy upon that growth and development.

Chu Do we understand why the same tumor that presents in a young child as opposed to an older adult does respond so differently to chemotherapy and to treatments in general?

Kupfer I don't think we have a clear understanding. We certainly do not have an understanding of a pediatric disease in terms of exposure in the same way we fully know that the exposure to cigarettes smoking is tied to lung cancer. There is none of the certainty, no strong associations of any kind of environmental or virus exposure leading to cancer in pediatrics. Rather, I think most people would believe that most pediatric cancer is simply a consequence of normal growth and development gone awry, such that would probably occur in a fixed rate of occurrence that we probably have no ability to control.

Foss We would like to talk a little bit more about some specific approaches for pediatric cancer after we take our break. You are listening to Yale Cancer Center Answers and we are here with Dr. Gary Kupfer discussing treatment and care for children with cancer.

*Medical
Minute*

It's estimated that over two million men in the US are currently living with prostate cancer. One in six American men will develop prostate cancer in the course of his lifetime. Major advances and the detection and treatment of prostate cancer have dramatically decreased the number of men who die from this disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests; a physical exam and a blood test. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for prostate cancer. The patients enrolled in these trials are given access to experimental medicines, not yet approved by the Food and Drug Administration. This has been a medical minute and you will find more information at [yalecancercenter.org](http://www.yalecancercenter.org). You are listening to the WNPR Health Forum from Connecticut Public Radio.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by my co-host Dr. Ed Chu and Dr. Gary Kupfer, Director of the Yale Cancer Center Pediatric Oncology Program. We talked about how pediatric cancers are different than adult cancers in the first part of the program. Gary, can you talk a little bit about specific treatments? Are there specific new drugs that have been developed for pediatric cancer?

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Kupfer We talked a little bit before about how the first clinical trials were performed in pediatric cancer going back now about 60 years, and rather than there being the great dramatic breakthrough that one hopes for, certainly it's been kind of a steady, incremental approach that's yielded the great advances in pediatric cancer over the years, and actually continues to this day. It's been the rationale use of the drugs that have been around for many years, using them in different ways, pushing the envelope of increased dosage and timing of these drugs and figuring out how best to use them. Now, we have taken the experience, of course, of the adult oncology program and in using some of the new drugs that come our way. In the last couple of years, one of the most dramatic advances has been the use of Gleevec, which has been used of course in adult CML, and adapting it to use in pediatric ALL in one of the subtypes, and it's been a dramatic turn around, but in general, the greatest advances that we have been able to make have really been in the continued incremental approach that's got us to where we are today.

Chu Gary, in the adult world, there are a number of large cooperative groups in the United States that play a key role in helping to identify and develop new treatment regimens for older patients. Is there a similar type of collaborative, cooperative group in the pediatric oncology world?

Kupfer Pediatric oncology is largely under the auspices of the Children's Oncology Group, which is, as we mentioned, a national cooperative group that seeks to get all the pediatric treatment centers to use the same treatment protocols nationally. It's really a key in pediatric oncology obviously because we are talking about a number of patients, which is far smaller than the numbers that you will see in the adult oncology world. It's critical that we get together just so that we can pool and get the statistical power we need in order to figure out that these treatment protocols are going to work.

Foss Are most children with cancer actually treated on clinical trials?

Kupfer Not necessarily, however, most patients with pediatric cancer are treated at major centers. Pediatric clinical trials generally have a great number of stipulations in order to get patients on trials, in order to make things uniform nationally, so that people can understand how best to take care of these children. On the other hand, every child who comes in with the diagnosis of cancer has basically the latest protocols that we use even if they are not actually officially entered on trials. Every pediatric tumor has a committee at the national level in which we participate. I for instance, participate in the National Hodgkin's Committee and so twice a year we get together at our national meeting and we discuss how the current protocols are going and how best to take care of the various subtypes, for example, with Hodgkin's disease.

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- Chu So it sounds like in your own clinical world you focus on lymphomas, but can you tell listeners out there what the different types of diseases are that you tend to focus on in your own clinical practice?
- Kupfer My clinical practice is informed by some of the research that I do. I focus on the genetic predisposition syndromes of cancer and some of those genetic predisposition syndromes, such as the one I focus called Fanconi anemia, are diseases which predispose children to getting leukemia. So, I tend to focus on leukemias and lymphomas. The fact of the matter is that our numbers, being relatively smaller than say the adult world where one can completely focus on prostate cancer for example, means that we really have to be able to understand and diagnose and treat all pediatric patients with cancer because we do have to take care of all comers.
- Foss You are talking about genetic predisposition to cancer in children. What percentage of children actually has one of these genetic syndromes?
- Kupfer These are very rare diseases, upwards of one out of a million, one out of a hundred thousand, in that range. What they do is that they inform on more general ideas and processes of cancer and the biology associated with cancer, and they serve as models for understanding these processes. Take the disease I work on, as I mentioned Fanconi anemia, I started working in this area about 17 years ago, and at that time it was thought be an obscure genetic disease, well over a period of years that I worked in the field, there are all these connections being made to breast cancer genes, and so the adult oncology world has been drawn into the particular field I work on.
- Foss Not only that, but there has been the Wilms tumor gene and the retinoblastoma gene, both discovered in pediatric cancers and both important in many adult cancers as well.
- Kupfer Absolutely. So, these processes of how cancer is formed and how cancer might respond to a therapy, these are threads and lessons that run through both the adult and pediatric oncology world.
- Chu Gary, with respect to Fanconi anemia, the disease that you work on, how many children are affected with that disorder?
- Kupfer It is a rare disease; perhaps one out of three hundred thousand worldwide. So a relatively rare disease; however, some of the genetic subtypes of Fanconi anemia are actually caused by mutations in the BRCA2 gene, the breast cancer gene, and it's really amazing how these

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connections are being made, so much so that the biology that we have learned from working on Fanconi anemia now helps us understand in general the breast cancer genes and these processes of how cancer actually gets formed. So the actual numbers per se of these rare diseases are small, but the affect that they impart on our world of oncology is really dramatic.

Foss Are there typical genetic tests that a child will undergo after the diagnosis of cancer, in other words do you routinely look for some of these rare genes?

Kupfer We do, we also look at the whole child, because many of these genetic syndromes do have some clues. It might be some physical findings that we see in the children, it might be the family history of multiple cancers showing up in young people within the family, and so we try to take those clues rather than putting patients through a complete battery of tests, which would probably end up clogging all the laboratories within our hospital and nationally. We try to do things in a fairly measured way so that we can more logically figure out what's going on with our kids.

Chu Is there an increased risk for say children who have Fanconi anemia down the road to not only perhaps develop leukemia, but breast cancer and/or ovarian cancer if they were a woman?

Kupfer These patients, up until a few years ago, were actually not surviving into adult. It's only been with the understanding that these kids have to undergo bone marrow transplant that people are actually surviving to adulthood. Curiously, they are getting breast cancer, but they are also getting lots of other solid tumors of the head and neck and of the genitourinary tract. It's kind of an open area as to just what kinds of cancers eventually these kids will get once they grow up. Of course just getting a bone marrow transplant to cure their propensity to getting leukemia is certainly not going to do anything about their solid tumor risks. So, this is really an evolving field right now in 2009.

Foss I think an important point in this story for our listeners Gary, is the whole issue of supporting research in rare diseases. You know, these diseases that are very infrequent, you could say, well why should we continue to put money into research? But you have talked to us about a lot that we have learned from this and ways that we have significantly affected the lives of these children and as you say, with transplant, allow them to have a longer life.

Kupfer It's interesting because I lecture medical students and residents about cancer biology and I always put up a list, a huge list, of these rare genetic diseases, but alongside the list, there is a list of different biologic processes that are understood as a result of studying these rare

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diseases and this is amazing, it's like a hall of fame of cancer biology in terms of what we are able to adapt from studying these rare diseases. It's a real lesson that understanding and looking at basic signs of these rare syndromes led to an explosion of scientific knowledge and cancer biology.

Chu Certainly, as you had mentioned earlier Francine, the retinoblastoma story, really kind of led to the whole molecular genetic basis for cancer, and our understanding of how cancer arises genetically.

Kupfer And as we mentioned, the retinoblastoma gene being a perfect example, going back almost 50 years, a rare pediatric cancer showing up in about 2% of our patients, which is a malignancy of the eye, of the retina. It is a testament to where we need to be focusing our resources, and the kinds of areas we need to be looking at.

Foss I think the other important point, from the point of view of our listeners to understand, is that there is a tremendous amount of cross fertilization between pediatric oncology and adult oncology, in that we all attend the same meetings, the American Society of Hematology, the American Society of Clinical Oncology, as well as the American Association for Cancer Research meetings. So there are opportunities for the pediatric research scientists and pediatric oncologists to interact with the adult medical oncologists and bring the whole field forward.

Kupfer That's absolutely right, and in fact, many of my scientific collaborators are adult cancer clinicians and biologists, but also some of the lessons we get out of studying a rare disease, like for example of Fanconi anemia, has implications for therapy as well, so much so that we are actually working on adapting some of the lessons we worked on in Fanconi and we have been working on a strategy to treat resistant cancer, which is actually more likely to be an issue in the adult oncology world. We have a number of other institution trials that we are promoting. HERO'S Clinic is very active at trying to understand the neurocognitive effects of our therapy in radiation and chemotherapy. We also have several labs within our section that are kind of at the pre-clinical stage of trying to figure out new trials that will attack resistant cancer. We have Dr. Dhodapkar who works on dendritic cells as an immune therapy model to try to go after resistant cancer and my lab in particular is working on a viral protein that we hope will target resistant cancer as well.

Chu Great. We look forward to having you back on a future show and hear all the great advances. You have been listening to Yale Cancer Center Answers and we would like to thank our guest Dr. Gary Kupfer for joining us today. I am Ed Chu from Yale Cancer Center wishing you a safe and healthy week.

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If you have any questions or would like to share your comments, you can go to yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past program. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.