

Yale CANCER
CENTER

answers

WNPR Connecticut Public Radio



Hosts

Edward Chu MD

Chief of Medical Oncology

Kenneth Miller MD

Director of Supportive Care

Pediatric Oncology Research

Guest Expert:

Gary Kupfer, MD

*Associate Professor of Pediatrics, Yale
School of Medicine*



Yale Cancer Center Answers

is a weekly broadcast on

WNPR Connecticut Public Radio

Sunday Evenings at 6:00 PM

Listen live online at

www.wnpr.org

OR

Listen to archived podcasts at

www.yalecancercenter.org

Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center, and Dr. Miller is a Medical Oncologist specializing in pain and palliative care. He also serves as the Director of the Connecticut Challenge Survivorship Clinic. If you would like to join the discussion, you can contact the doctors directly at canceranswers@yale.edu or 1-888-234-4YCC. This evening, I will be sitting in for Dr. Chu and Dr. Miller. I am happy to welcome Dr. Gary Kupfer. Dr. Kupfer is Chief of Pediatric Hematology and Oncology at Yale School of Medicine.

- Barber Gary, let us start at the beginning. Where did you go to college, and where did you receive your medical training?
- Kupfer Well the first place that I got an appreciation for cancer and taking care of patients, was when I was an undergraduate at the University of Florida. That was where I first started working in a laboratory in cancer biology, back when I was a sophomore.
- Barber Did the science grab you at first or was there a personal reason that you got involved in cancer research?
- Kupfer I've always been someone who is interested in a lot of different things, and the idea of doing cancer research in the laboratory, but also having the ability to combine that with taking care of patients, is what really attracted me.
- Barber So you decided to go to medical school. Where did you do that?
- Kupfer I went to Baltimore, to Johns Hopkins University, which really got me started and interested because it is a place that has a great tradition of training both physicians and scientists, and molding those two together.
- Barber Then what happens generally is that you start to narrow things down, you go through medical school and then you pick a residency. What did you do for your residency?
- Kupfer I went to do my training in pediatrics at the Children's Hospital in Philadelphia, again a place that has a long tradition of training academic physicians.
- Barber Did you know then that you wanted to be involved in working with cancer and children, or were you thinking pediatrician at first?
- Kupfer I really conjured both of them in my mind, and the idea of combining multiple professions under one roof, that is academic pursuits in the laboratory and also taking care of children, which I have had a great affinity to for many years, was very exciting to me.

2:35 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-13-08.mp3

Barber It is amazing work to be able to do, for really the most vulnerable population.

Kupfer Absolutely, and also just the idea of being able to interact with kids is a great joy everyday.

Barber I find pediatricians are always quite wonderfully social beings and love to be with the kids. Then you focused more on blood diseases, correct?

Kupfer Actually, pediatric oncology and hematology are joined as a subspecialty, for many reasons, one is because the most common pediatric cancer out there is leukemia, which of course is cancer of the white blood cells specifically, so it is representative of why hematology and oncology have been joined under one roof.

Barber Me being a layperson, tell me a little about your specialty.

Kupfer Pediatric cancer, oncology and hematology, doesn't represent a very common disease. In fact, only about 15,000 to 20,000 patients a year get diagnosed with having cancer in the pediatric population in this country. They are around 50 times less common and less frequent than adult cancer. On the other hand, you can imagine what happens when a child gets cancer within the family. It is obviously not just the patient, but it affects parents and extended family.

Barber I am aware of this because friends of our family just went through this exact experience, and it is absolutely devastating. That is a great way to start, as you describe it. It is fewer cases than adult cancer, but for a child it can be a situation where you have a child that is vital and active and doing amazing things even, and then all of a sudden they are in the hospital very sick. The family, and as parents, you are devastated, but you need to soldier on and help this child get well.

Kupfer That is exactly the way we put it to the parents. It is absolutely the most devastating moment of their lives up until that point in most cases, and you have to marshal the forces together and make it clear to the parents that they are part of the team. They are just as important to their kid getting better as the doctors, nurses, pharmacists and all the other people that are taking care of their child. They are just as important because the bulk of the time that goes into the care of that child is spent at home. It is really critical for parents to be on the same page as the rest of the medical team and active participants in their child's care.

Barber I have heard great things about what goes on at Yale with respect to setting up a support system. You have a team approach, but there is also setting up a system of support. Walk me through what the procedure is when you do have that tough conversation with parents and say, here is the diagnosis. What are the basic diagnoses that you work with, and then take me through what happens?

6:11 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-13-08.mp3

- Kupfer The two most common diagnoses that we encounter are pediatric leukemia and brain tumors. Together, those two diagnoses make up about half of the patients that we take care of. Actually, it turns out that a great deal of lead-up time is spent in order to figure out what a patient might have. Again, these are relatively rare diseases, and therefore we take a great amount of care to be sure what we are dealing with. That means a variety of different diagnostic procedures, and again, a team approach, which might include the skills of a radiologist, a surgeon or pathologist, all of whom have to work hand in hand to get a hold of biopsy of the tumor or analyze a sample that we sent to the lab after a bone marrow sampling. So, everybody really needs to work together. In fact, we have a number of conferences where we get together in order to discuss the diagnosis and to be sure what we are dealing with. There is a great deal of preparation and lead-up time that goes into, as you put it, that very difficult conversation that we have with parents.
- Barber You are interacting with a family physician who has noted something wrong and has sent the child to you for a diagnosis.
- Kupfer Absolutely. As you can imagine, with pediatric cancer being so rare, this is not the sort of diagnosis we can detect early in the same way one might be doing breast cancer self-exams or yearly exams for prostate cancer. This is indeed picked up in most cases in the primary care provider's office, either through a blood count done in response to an acute illness, or the pediatrician picks up an abdominal mass. We are almost always referred patients where the pediatrician has detected some problem.
- Barber It is so rare that I would imagine there are cases in which you find that it is not cancer.
- Kupfer That does happen, and believe me, we are more than glad when that does happen. We are also very aware that we have to be ready to take charge and to help these families through what is definitely a devastating diagnosis and help them realize that there is a great deal of hope out there for the families and their children.
- Barber Let us back up a little bit. Tell me about how you came to join us here in New Haven at Yale.
- Kupfer After my training was completed at Harvard Medical School in pediatric cancer, I took a faculty job at the University of Virginia, where in addition to taking care of patients, I opened up my laboratory in cancer biology. But an opportunity arose here to take charge of the pediatric oncology program, and I was attracted by the idea of joining a medical school in which there is just incredible depth and breadth of cancer research going on, which actually fit in very nicely with the particular cancer research that goes on in my laboratory. I was very attracted for

that reason. There is also an incredible amount of energy here in the Yale community, with the construction of the new Yale Cancer Center Hospital and an incredible surge of activity going on in building both the clinical and the scientific research arenas.

Barber I would imagine that doing research, something I know very little about, but from what I have read, it really involve a lot of collaboration, does it not?

Kupfer Absolutely. It becomes clear when one is doing work that you really have to rely on people, not only for research materials, but also for the interchange of ideas. Some of the most fruitful scientific interchanges I have had come over a cup of coffee or just leaning against a wall in the hallway talking to colleagues. It really is important to have colleagues with whom you can talk, with whom you can have informal interchanges with.

Barber The setting in the lab I would imagine it that you are mainly doing kind of mundane work, and then all of a sudden there is that "Wow" moment. Is that true, are there moment with people high-fiving?

Kupfer I would say that those high-five moments come extremely infrequently. The norm is more that it is very tiny building blocks one after the other, in fact, building blocks that are based on all the little blocks that are placed by numerous people all over the world. We go to meetings, we read literature, scientific literature, and we try to learn from each other. No one has ever accomplished great things in the laboratory in a vacuum. It is all based on people who have done work over many years.

Barber That is interesting, you hear about this medical conference or that medical conference, and that is why sometimes Ken or Ed can't be here, but that notion of doctors and researchers giving talks, as a situation that may inspire you, is fascinating. Is that kind of the way it works?

Kupfer Absolutely. I have certainly gained ideas in my research by listening to other people give their talks on their own research, but again, it comes from informal meetings, meetings in hallways, over cups of coffee and people making little strides over many years and adding them all up together. People work together and form groups, and bring it back to the clinical side. There is probably no better example of people making little strides and adding them up over the years, as a great advancement Spain made in pediatric cancer treatment. If you look back into the history of pediatric cancer treatments, 60 years ago every patient with pediatric leukemia died. There was 0% survival.

Barber And that was just 60 years ago; 0% survival.

13:11 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-13-08.mp3

Kupfer It is a great example of a medical miracle when you think about it. People have these very negative connotations and ideas of what chemotherapy means. They think about bald people, people throwing up all the time, but in fact, chemotherapy in pediatric leukemia specifically, has meant going from 0% survival, in the specific case of pediatric lymphoblastic leukemia, to around 80% to 85% survival in the year 2008. It really is an amazing story but that did not come overnight, it came from little building blocks of people getting together, working together and forming national groups. People were treating all their patients in the same way, and then putting all the data together in order to figure out new and improved ways to treat their patients year after year after year.

Barber That is fascinating. Let us come back in just a minute and talk some more about how we have gone from 0% survival to 85% survival. Correct?

Kupfer Yeah, around 80%.

Barber 80% survival in only 60 years, and we'll talk about how those building blocks work. You are listening to Yale Cancer Center Answers.

Medical Minute

Breast cancer is the second most common cancer in women. About 3000 women in Connecticut will be diagnosed with breast cancer this year. But, earlier detection, noninvasive treatments, and new therapies are providing more options for breast cancer patients than ever, and more women are able to live with breast cancer than ever before. Beginning at age 40, every woman should schedule an annual mammogram, and you should start even sooner if you have risk factors associated with breast cancer. Screening, early detection, and a healthy lifestyle are the most important factors in defeating breast cancer. Clinical trials are currently underway at federally designated comprehensive cancer centers such as the Yale Cancer Center to make new treatments, not yet approved by the Food and Drug Administration, available to patients. This has been a medical minute, and you will find more information at www.yalecancercenter.org. You are listening to the WNPR health forum from Connecticut Public Radio.

Barber I'm happy to be joined today on Yale Cancer Center Answers by Dr. Gary Kupfer, who is joining Yale. How long have you been at the Yale Cancer Center?

Kupfer I have been here six months.

Barber Welcome to New Haven.

Kupfer I am finding my way around finally.

15:38 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-13-08.mp3

- Barber It is great to have you here. You have a great reputation for pediatric cancer research and you actively explore how deficits in the human genome lead to cancer. Let us finish up first what we were talking about before and then go into the genetic component, or maybe those two things tie in together? Let's go back 60 years ago, what were some of the first things that started to cut away at those very difficult figures of losing 100% of patients with that particular kind of leukemia? What happened first and then what is going on now?
- Kupfer It was the realization of the use of chemotherapy that really made these great inroads into the treatment of pediatric cancer, pioneered by people like Dr. Sidney Farber at the Dana-Farber Cancer Institute, where the first clinical remissions in childhood leukemia were achieved. Then again, it really required the cooperation of pediatric oncologists all over the world. They were cooperating these national groups where people all agreed they were going to treat patients in the same way, and not be selfish with their information, but rather put it all together with everyone else's information and then figure out statistically what would be a better and more rational way to go.
- Barber Give me a little background on chemotherapy. Had it been used more on adults before that, or was chemotherapy fairly new 60 years ago?
- Kupfer It was still fairly new. In fact, some work in chemotherapy was being done at Yale New Haven Hospital, using agents which came out of World War I; the mustard gases which were used on the battlefield. Some of the earlier work on mustards in chemotherapy was actually done right here, but some of the other new chemotherapeutic agents were pioneered by Dr. Farber up in Boston.
- Barber Dana Farber Cancer Institute has a great reputation, but it is interesting to hear now why it has such a good reputation. Dr. Farber was really the first one to start having success with this?
- Kupfer That is right. But back then, his first idea of course was using one drug to treat patients. Although you could put a patient with leukemia into remission, where you could not see the leukemia anymore, it was clear that only one drug could not cure a patient with leukemia, you had to add other drugs together with that one drug. It really was an example of what is true about cancer; it is a disease caused by defects or changes within the genome. This kind of leads us back to what you were getting into, which is how cancer is a problem with changes or defects in the genome, changes in critical genes within our DNA leading to either a growth advantage or cancer or a decreased amount of cell death in that particular tumor.
- Barber It always comes down to this and is what you guys are always wrestling with, there genetic abnormalities that you are born with, and also environmental factors. Is that a good way to put it?

19:19 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-13-08.mp3

Kupfer It is always good to remember that we all are born with one disadvantage in terms of leading to cancer. In fact, we all have a major risk factor. 100% of us have the risk factor of aging. Aging leads to cancer.

Barber Okay.

Kupfer We all have a lifetime risk of about one in five of getting cancer, in those terms, cancer is part of our normal biology. Down on the molecular level, if you think about the way our DNA is made and managed within each cell of our body, there is actually a fixed error rate in the way DNA is managed and made, so much so that cancer is actually thought of in that way; cancer is a part of our normal biology. That is why aging, which represents potentially an accumulation of genetic change, goes hand in hand with cancer.

Barber Tell me about what it is that you have learned on the genetic level when a child gets cancer.

Kupfer Because children are undergoing such rapid growth from the time of conception in utero, all the way to birth, and then in the first years of their lives, it is clear that in order to have growth you need cell division and to have cell division, you have to have duplication of your genome, indeed of your DNA. It goes back to the idea that there are fixed error rates that go on with your DNA that you simply cannot avoid. Now, we have very elegant means of preventing those errors and screening for errors, but even with the best systems of preventing errors, there are still going to be errors that sneak through, and they are unavoidable.

Barber Talking about chemotherapy, what is actually going on there?

Kupfer There is actually a wide range of different chemotherapy agents. Some of them directly inhibit the way DNA is made and some of the drugs chemically modify DNA leading to the destruction of the cell triggering cell death. The whole idea of chemotherapy is not to use one means of subverting the cell, but multiple means because at its very heart, very nature, cancer has originated from a cell that has found a way to escape the means of regulating cell growth. That means that cancer cells have been able to avoid regulation, and once it does that, it has already become genetically very able to avoid means of dying.

Barber It is a rogue agent.

Kupfer So it actually has a greater means of adapting to being killed by a particular agent.

Barber Because it is operating off on its own now, is that the way you are putting it?

22:23 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-13-08.mp3

Kupfer In many cases it is able to genetically adapt better than your average cell, just by its very nature of having escaped our normal means of cancer prevention.

Barber Is what you are working on now, the correct combination of these agents, or are you looking into trying to develop new agents?

Kupfer The basic things that we work on in my laboratory go back into the tradition of cancer research, looking at these rare genetic diseases of cancer susceptibility. We are working on a particular genetic disease called Fanconi anemia, and Fanconi anemia is of interest to us because although this is a rare disease, these are children who are born with a greater susceptibility to getting leukemia, and if one looks at the history of cancer research, we have learned a lot about not only cancer, but normal biology by studying how and why genetic diseases lead to greater incidence of getting cancer. In this particular disease, Fanconi anemia, we have learned that these patients are born with defects in DNA repair and surveillance of the genome, and by having defects in repairing their own DNA and defects in their genome, that triggers a greater incidence of getting cancer.

Barber How much is the human genome project helping your work?

Kupfer The genome project has revolutionized what we, and pretty much everyone in the world does, and that is there is really no gene that is not heard of sitting in a database somewhere, it is a matter of going there and finding it and pulling it out. It has traversed a lot of technical problems that people have had in pulling out DNA sequences. It has narrowed down the amount of time that it takes from understanding potentially what genes are involved to actually being able to study them. You can pull out whatever genes you want to look at within a matter of days versus a matter of months or years that it used to take.

Barber How much information do you need to narrow it down so it's not like searching for a needle in a haystack?

Kupfer One gets clues from other people's work and colleagues with whom you are actively working together on projects. You realize that every good research project that answers a question only leads to more and more interesting questions down the line.

Barber This has been so fascinating. I understand this a lot better now. It sounds like really exciting stuff. There have been such amazing strides in 60 years, and you must be at a point now where things are really rolling. What are looking to accomplish in the next two or three years?

Kupfer Our work on this genetic disease is really focused on the very basic biology of the disease, and how that basic biology causes cancer, and also what normal role it plays in our cells. What we have learned from this genetic disease is that patients with the disease have problems dealing with genetic damage. We are learning

ways to try to adapt that to make cancer therapy more effective. In addition to our very basic studies on this genetic disease Fanconi anemia, we have started a parallel project in order to tweak DNA repair systems in cancer cells. We have a very active project going on, which we hope to use clinically in the next few years, to make resistant cancers more amenable to cancer therapy.

Barber So you are finding agents that change the way cells react?

Kupfer Absolutely, and in this particular project I am talking about, we have adapted a protein made by a virus in order to subvert the way cancer cells are resistant and turn them into sensitive cancer cells, make them more amenable to treatment.

Barber It is amazing that when we talk about agents, that it starts with mustard gas, 60 years ago.

Kupfer Actually, going back farther it would be about 90 years.

Barber So you continue, based on all these conversations, to look at what things have been found that are going to turn off, or go after, those rogue cells so they cannot do what they want to do.

Kupfer Yes, make a cancer cell become more open to being treated using standard chemotherapy. It is amazing the landscape of cancer biology right now and the means of trying to treat cancer. There are all kinds of new and interesting ways that people are devising to try to get at particular cancers. We may have to fashion and tailor a unique way of attacking cancer for all the variety of different cancers, and cancer of course is not just one entity. It is many different kinds of diseases.

Barber Dr. Gary Kupfer it has been really interesting speaking with you today, and I applaud your work. We started this by talking about what a devastating conversation it is to have with the parents, but you know, having folks such as yourself and your team working on these diseases, it is going to make me sleep better at night. It has got to be exciting for you just to be able to do this for people.

Kupfer I have one of the best jobs in the world, and that is getting to take care of patients, work in the lab and teach. It is a great job, a job which is intense at times certainly, but one which I think is a great privilege to have and I enjoy very much.

Barber Thank you for joining us on Yale Cancer Center Answers. We wish everyone a safe and healthy week.

29:08 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Apr-13-08.mp3

If you have questions, comments, or would like to subscribe to our podcast, go to www.yalecancercenter.org where you will also find transcripts of past broadcasts in written form. Next week, you will learn about the treatment of testicular cancer with Dr. Kevin Kelly.