

Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Ken Miller. 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. Miller is the Director of the Connecticut Challenge Survivorship Program and he is also the author of "Choices in Breast Cancer Treatment." If you would like to join the discussion, you can contact the doctors directly at canceranswers@yale.edu or at 1-888-234-4YCC. This evening, Ken welcomes Dr. Peter Marks. Dr. Marks is an Associate Professor of Hematology at Yale School of Medicine, and an expert in the treatment and research of leukemia.

- Miller Peter, you and I have talked several times about acute leukemia, and about leukemia in general. Let me start out with the first question. People talk about chronic leukemia, and they also talk about acute leukemia, what is the difference between the two?
- Marks Acute and chronic leukemias, although they are grouped under the general heading of leukemias, actually represent distinct disorders that manifest in different ways and require very different treatments. They also have very different outcomes over the course of time. The acute leukemias are disorders, which means when they arise, if they are not treated, will rapidly take someone's life. The chronic leukemias, when they arise, tend to take a few years or more before something major happens. In fact, for certain types of chronic leukemia such as chronic lymphoid leukemia, no treatment may be necessary for many, many years.
- Miller One of the terms, or concepts, that I have heard is that chronic leukemia, or certain leukemia, is a disease where you have accumulation of cells; cells live too long. For other leukemia, the cells are growing too rapidly, is that a fair concept?
- Marks The way I would think about it is somewhat like that. We can think about the fact that in acute leukemias, the cells start to divide and they continue to divide without the normal process that would put them in check, and they just keep accumulating. The cells accumulate and accumulate, some die off, but way too many are being produced until one has bone marrow that gets filled up with these abnormal cancer cells. In the chronic leukemias, the cells that tend to build up often look like they are normal cells, and to a certain extent, there can be quite a number of years that go by before the bone marrow gets filled up with these abnormal cells. In that case, it is that the cells over the course of time go from being somewhat like normal cells, to abnormal cells, or, over the course of time, the cells build up more gradually. In some ways they are cancers that have similar issues, but with some subtle differences in how the cells build up over time.

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- Miller Let us focus on acute leukemia, can you tell us what the categories of acute are?
- Marks The two major categories of acute leukemia are acute myeloid leukemia, or acute myelogenous leukemia, which are the same, and acute lymphoid, or acute lymphocytic or lymphoblastic leukemia. The difference between those has to do with the type of normal cell that is the counterpart to the leukemia cell. There are two major types of white blood cells that help the body to fight infections. One of them is the myeloid cells, a subtype of them is called granulocytes, and those are neutrophils that help protect the body from bacterial infections. Those myeloid cells are involved in the normal day-to-day eating of bacteria and protecting the body from the pathogens in the world around us on a day-to-day basis. They are like foot soldier cells that make sure our bodies are not invaded by bacteria. The second are lymphoid cells, and they are a different type of cell; there are B-cells and T-cells that cooperate to give us immunity on a more complex level. They create antibodies and some of these cells actually work to kill cells directly. That's the lymphoid arm, and those lymphoid cells can also give rise to leukemia. We tend to talk about acute myeloid leukemia, that is the one arising from these kind of foot soldier cells, and acute lymphoid leukemia, arising from the cells that normally go on to make immune responses that lead to antibodies or to more prolonged responses of the immune system.
- Miller I have to tell you, that is the clearest explanation I have ever heard. Let's focus throughout the rest of this program on acute myeloid leukemia. I think a lot of the audience knows, but my wife Joanne had acute leukemia nine years ago, and thankfully she is doing well. How many people are diagnosed with acute myelogenous leukemia every year?
- Marks Acute myeloid leukemia is diagnosed with about 12,000 cases in the United States each year. Overall, that makes up about somewhere in the order of 30% of the overall leukemia diagnoses.
- Miller Is it smoking, is it cellphones, do we know what causes it?
- Marks There are certain things that have a known association with acute myeloid leukemia. We know that exposure to large amounts of radiation, such as people who were exposed to the atomic bombs in World War II, had an increased risk of acute myeloid leukemia, and people around atomic accidents. There are certain chemicals such Benzene that have been associated with increased risks of acute myeloid leukemia. Those are kind of environmental factors, but they account for a very small portion of acute myeloid leukemia. The two things that actually lead to acute myeloid leukemia, that probably are more of note today, would be acute myeloid leukemia arising from other

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hematologic disorders, including things like myelodysplastic syndromes or other myeloproliferative disorders. Those are probably a topic for another day, but the other are therapy-related acute myeloid leukemias. Those are leukemias that develop after cancer chemotherapy for some other disease. One of the remarkable benefits of adjuvant chemotherapy, for instance for breast cancer or for other diseases, has been that we cure many more people who would not have been cured in the past. Unfortunately, one of the side effects is that a small portion of those people, nothing that would negate the benefit of that adjuvant therapy, but a rather small portion will develop acute myeloid leukemia at a rate that is perhaps two or three times that of the general population. Those people represent a category of people who are at risk, people treated with prior chemotherapy for acute myeloid leukemia. Certain agents are more associated with it than others.

- Miller When you are seeing a new patient with acute leukemia, typically, what are the symptoms that bring them to see you?
- Marks Sometimes there are no symptoms at all. Occasionally, somebody just goes to the doctor and is noted to have a very low white blood cell count, or a high white blood cell count, and that is one thing that people should be aware of. Many people think that leukemia is too many white blood cells in the circulating blood, but that is not the only way it presents; some people have not enough of the normal white blood cells because all of leukemia cells are gathered up in the bone marrow and not in the circulating blood. The most common presentations are people who develop recurrent infections; somebody who goes to the doctor with an upper respiratory tract infection, the doctor thinks they have bronchitis and gives them a course of antibiotics, but it never really gets better. Eventually, after two or three attempts like this, they come to get a complete blood count performed and that leads the diagnosis. The other reasonably common way is that somebody develops evidence of some type of bleeding, either they start to have bleeding from their gums that they have never had before, or they look down and they notice that they have a lot of bruising and they have never bruised like this before. Obviously, in both of those cases, those are very nonspecific.
- Miller I want to ask you a related question, in seeing this group of people who are told they have this serious disease, what does the patient say? I mean, I can tell you what ours was like, but what are people's reaction when all of a sudden they hear this news?
- Marks There is a diversity of reactions. Overall, I think most people are somewhat stunned. One of the first reactions often is, why me? What did I do wrong to have this happen? And a fair amount of my job is reassuring people that acute

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myeloid leukemia, unlike certain other types of cancer where we know that there are behaviors that we can modify, in this case there is no modifiable behavior, so it is a matter of reassuring them that this is not anything that they have done wrong. Another very common response is, "Oh my goodness, are my children going to be affected by this, is this a genetic thing that I am going to pass on to my children?" To the best of our knowledge at this time, this is not the case. When one has this, it is something that is just in our blood cells, the blood forming cells, and not in the rest of our genes that we can pass on. It is true that it is possible that there could be some predisposition that could be passed on in certain cases, it is possible, but we do not think that is the case in the very large majority.

Miller I am going to ask you a question that I think some people think about, but do not bring up, truth or myth, is leukemia, cancer, contagious?

Marks It is not. In this case, acute myeloid leukemia is not a contagious disease. There are certain types of leukemia, mainly of the lymphoid variety, that we see associated with viruses, but in the case of acute myeloid leukemia, there is not any evidence that there is anything that could be contagious here. Frankly, even if you were to try to pass it, the fact is that a normal immune system sees these leukemia cells and kills them, which is one of the ways that we can look for therapy, is that the normal immune system kills leukemia cells.

Miller Let me ask you another question that I believe patients ask, or certainly think about, they might look at you and say, "Dr. Marks, is this a curable disease?" What would you tell them?

Marks I try to be honest with patients that by and large, in younger people, we cure a reasonable percentage of the patients who present with acute myeloid leukemia. We do not cure everybody, and one of the important things about getting treated for acute myeloid leukemia is understanding the exact type of leukemia to the best of our abilities, in the year 2008, that we understand so that we can properly prognosticate and properly treat with a level of aggressivity that matches the disease present to maximize the chance of cure. In people with reasonably good prognosis for acute myeloid leukemia, and there are certain types that have a very good prognosis, we cure 70% or so of people of the disease. In older people, say perhaps over the age of 75, we really do not cure very many at all, but that does not mean that there is nothing to be done. We do have therapies now that, we believe, prolong life and improve quality of life, so it is not that there is nothing to be done, it is just that we are not aiming for cure in the older population of individuals; we are aiming to help them for the longest period possible.

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- Miller In the couple of minutes before our break, let's talk a little bit about an older population. For example, you see an 82-year-old who presents with acute leukemia, what would be your approach in terms of treating them, what are some of the advances?
- Marks First of all, when I see an 82-year-old I try to get to know them as a person to understand what they are doing in their lives, how active are they, what are their values, and what are they looking for out of the coming years. Some people will say, "I mainly want to just be as comfortable as I can, I do not want to be troubled with treatment, can you just make sure that the next months of my life are as trouble free as they can be?" Other patients, who are very active, and I have seen people, who are still very, very active in their communities at 82, and some are working still, and those individuals want to have as long a life that they can with this disease in check. I try to counsel them that we probably will not cure them of the disease, but the options that are available include various chemotherapies that can be given either by subcutaneous injection or by intravenous injection on a regular basis, but they do not eliminate the leukemia entirely, but in some cases they put it into a complete remission for a period of time and we think that in other cases they prolong life with an improved quality of life so that people can continue to do what they enjoy doing.
- Miller The concept you are bringing up essentially, which I think is the art of medicine, is getting to know people and helping them make these complex decisions. We are going to take a break for a medical minute. Please come back and join us and learn more about acute leukemia with Dr. Peter Marks, who is an Associate Professor at Yale School of Medicine.

Medical Minute

There are over 10 million cancer survivors in the US and the numbers keep growing. Completing cancer treatment is very exciting, but cancer and its treatment can be a life changing experience. After treatment, the return to normal activities and relationships can be difficult and cancer survivors may face other long-term side effects including heart problems, osteoporosis, fertility issues, and an increased risk of second cancers. Resources for cancer survivors are available at Federally Designated Comprehensive Cancer Centers such as the Yale Cancer Center to keep cancer survivors well and focussed on healthy living. This has been a medical minute and you will find more information at yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut Public Radio.

- Miller Welcome back to Yale Cancer Center Answers, this is Dr. Ken Miller and I am joined today by Dr. Peter Marks who is an expert in the treatment of leukemia from the Yale Cancer Center. Peter, let's go back to the scenario of treating an older person. You get to know them well, they get to know you,

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and they say, “Listen doctor, I want treatment.” What is new in terms of treating this disease?

Marks There are a couple of treatments that are out there, the most standard one might be low doses of a drug called cytarabine, which are given over the course of a number of days by subcutaneous injection. That might be considered almost a standard of care in the older individual, although there is really no absolute standard of care. In terms of therapies that are not on some type of clinical research protocol, and before I go any further I should say that I would encourage older individuals, when available, to look into clinical research protocols of new agents and combinations of older agents, but when that is not an option, the drugs that have been used more and more are drugs called hypomethylating agents. These are drugs that are chemotherapy drugs that have the potential to help these people without actually causing the typical side effects of stronger chemotherapies.

Miller So, I have got to ask you, what is a hypomethylating agent?

Marks These are drugs that have an effect on the DNA in these leukemia cells that, we believe, causes the re-expression of certain genes that have been turned off, and that the re-expression of these genes makes these cells essentially die off. That is the simple explanation of this.

Miller It is a fascinating idea. I guess in a sense what you saying is some genes have been turned off, and you are turning them on again, and that may kill cancer cells?

Marks That is correct, and actually, some of these agents probably work by more than one method. They may work on the cell's metabolism of the DNA and RNA contents; the various stuff that makes up the genetic material of the cell.

Miller From what you were saying earlier, unfortunately not everyone responds, but in terms of some of the patients whom you have taken care of, what kind of responses have you seen with this approach?

Marks We have seen about a third to perhaps 40% of people achieve some benefit in the over 70-year-old population, either of requiring a reduced amount of blood transfusions or another blood component platelets. Platelets are types of cells that are involved in clotting the blood, and they may have a reduction in the need for either the blood transfusions, or platelet transfusions. Somewhere in the order of between 10% and 20% percent of patients actually get a good, complete, or partial response leading to the absence of a need for blood transfusions, but moreover, leading to a restoration of their normal white

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blood cell function so that they are not at risk for infections and they can go about doing things that they normally do including swimming, jogging, whatever they want; things that they might have had to curtail because of the concern for infections or other problems.

Miller Let us switch topics to say a 41-year-old, my wife Joan was 41 when diagnosed, what is the typical approach there?

Marks For a 41-year-old the diagnostic piece becomes ever more important because understanding the risk category that that 41-year-old sits in will really determine our treatment approach. We generally divide patients based on chromosome abnormalities in the leukemia cells, again I want to reiterate this based on what we said before, this is not chromosome abnormalities in the rest of the body, it is just in the leukemia cells, but based on those chromosome abnormalities we divide people into favorable, intermediate, and poor risk disease. Depending on which category someone sits in, we can take an approach whereby we give standard chemotherapy, which takes on the order of somewhere between 4 and 6 months to administer, and then we call it quits. Sometimes, afterwards we have to give some maintenance chemotherapy in one particular type of acute myeloid leukemia, but the intense period of chemotherapy lasts for about 4 to 6 months, but those people in good risk groups, about 70% ,or even better in some sub, sub-categories, chance of being cured without having to do anything very heroic.

At the other extreme, the people with poor risk disease, we know that it is probably not worthwhile messing around with just giving them standard chemotherapy and then stopping, because the risk of relapse approaches 80% or 90% with just the standard chemotherapy approach. So, our approach to those individuals is to look to see whether they would be eligible for something called stem-cell transplantation, usually using a donor. Stem cell transplantation involves taking the white blood cells, or the cells that go on to form white blood cells, from one person and giving them to another person in order to be able to harness the immune effects of those white blood cells in killing leukemia. It also allows us to give high doses of chemotherapy while we are in the process of doing that, and so for individuals with high-risk disease or poor prognosis disease, we would often recommend an approach like this. Now for people in the middle, which of the approaches we will take depends on very specific risk factors; a standard chemotherapy approach or a more aggressive approach. Although for younger people, we are increasingly thinking about either stem cell transplant using the person's own blood cells for rescue, or using another individual's cells for rescue.

Miller There has been a lot of progress in chronic leukemia by using a drug, for example, called called Gleevec. How about for acute leukemia, are there

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certain targets that are arising, and what are the targets? Are there any in this case?

Marks

There are several targets. I will give an example of one target that has been targeted by an antibody, and another that has been targeted by a small drug. What a target is, is simply a part of the leukemia cell that is different enough, or unique enough, from other cells of the body so that we can make a medicine against it so that when it interacts with that target, it leads to cell killing; it does so more specifically than the rest of the cells in the body. What targeted therapies are, are ones that are able to kill one specific cell without harming the rest of the body, so we do not have to take the expense of harming other cells to kill that one cell. One specific way of going about this is to find cell surface properties that we can target with antibodies. Antibodies can be made in the laboratory and they can be used to target these cells surface molecules, or proteins on the surface of the cell. We can either attach radioactivity or other chemicals that kill cells to these antibodies, or in some cases the antibodies themselves lead to the cells dying. We can just target those cells without harming the normal cells, or minimally harming the normal cells. An example of that is a drug that has a long generic name, called gemtuzumab ozogamicin, and I think I even may have botched the second word of it, but the way we think about this is that this is a drug that we can give as an antibody to people. It targets these cells and there is a chemical portion of it that gets into the cell that gets to the genetic material in the cell, and kills it. The other example is one that targets a pathway of metabolism in the cell that is involved in cell signaling, and those are a class of drugs called farnesyltransferase inhibitors. One of them that has been in development is called Tipifarnib, and that is still not FDA approved, but there are other molecules like it that are also currently in development. Those drugs try to target a specific pathway that is abnormal in leukemia cells and tries not to affect them in the normal cells.

Miller

It sounds like things have changed. Let me put another question to you, looking back at your career, someone diagnosed when you first started, versus someone diagnosed now, how are things different for them in terms of how they will be treated, and even outcomes?

Marks

We have come a very long way in the past 20 years. Now we have a very good understanding of the importance of genetics, and the importance of the chromosome abnormalities in acute leukemia, and in acute myeloid leukemia our categorization schemes are now driven by the genetics rather than by how cells look. When I started doing this we would go to the microscope, look at how the cells looked under the microscope, and we would categorize them and say okay we are going to treat these leukemias. We did not make too much of a big deal about the chromosomes, and over the past 20 years we

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have increasingly understood how important the chromosome abnormalities are for how people will ultimately do, and how they need to be treated. This is also helping us to understand what is going on in terms of where we are going to go with the development of further therapeutics.

- Miller Along those lines, what research initiatives are you involved in, what is being done at our cancer center at Yale?
- Marks One of my particular interests is in helping older people with acute myeloid leukemia get towards cure, and right now we are starting the baby steps of rather than using completely novel agents, trying to take an approach where we take people who are in the midrange, that is between the ages of say 60 and 75, some of those would consider themselves young, and trying to take an approach whereby we lead to cures in a greater number of people. I think right now if we take a standard approach in say a 70-year-old, as I mentioned before, we do not really cure very many, if any of those patients. However, we believe that an approach whereby we move very rapidly from what we consider standard therapies that we use in younger individuals, without getting into many of the complications that can occur in older individuals, and then take them to a type of stem cell transplant where we use lower doses of chemotherapy, but rely on the immune component, that is the fact that somebody else's blood cells when they see leukemia cell kills them, that may be a very valuable approach.
- Miller We are coming down to the end here, but is that the mini-transplant?
- Marks That is a mini-transplant. Mini-transplant, or reduced intensity transplants, is exactly what you are talking about.
- Miller I have to say, it has been a really interesting half hour. What if patients, or family members, want to learn more about acute leukemia, what resources are available here at Yale or nearby?
- Markss At Yale we have the cancer center website, which is an excellent place people can go to look for information, www.yalecancercenter.org. I would also encourage people to look at the Leukemia and Lymphoma Society Website, which is an excellent source of information, it has been well vetted and I think patients get a lot out of that.
- Miller You have been listening to Yale Cancer Center Answers, and I want to thank Peter for being with us. Until next week, it is Dr. Ken Miller from the Yale Cancer Center wishing you a safe and healthy week.

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