

Dr. Peter Marks, Understanding Acute Leukemias January 17, 2010 Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Francine Foss. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing 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. Peter Marks. Dr. Marks is an Associate Professor of Hematology at Yale School of Medicine, Chief Clinical Officer at Smilow Cancer Hospital, and an expert in the research and treatment of leukemia.

Foss We are here today to talk a little bit about leukemia. I know there are lots of different types of leukemia, so can you just go through briefly what those different types are and how patients are diagnosed?

Marks There are two broad categories of leukemia; acute leukemias and chronic leukemias. Acute leukemias tend to have relatively rapid presentations. Usually patients are diagnosed because they present with something that becomes notable or noticeable to them, such as they develop bruising or bleeding, or they might develop recurrent infections or they feel fatigue. These are things that people generally cannot ignore and end up coming to the hospital to see a physician or going to their primary care doctor and seeing them. On the other hand, there are the chronic leukemias which tend to develop over the course of long periods of time. They tend to come to medical attention either incidentally or because somebody notices a lump or bump for instance, or they might notice abdominal fullness after they are eating, and that is a different type of presentation.

Foss Peter, given that both acute and chronic leukemias could be the subject of a whole show, today I would like to focus only on the acute leukemias. Could you backtrack just for one minute for our audience and explain what leukemia is?

Everybody knows leukemia is a disease of the blood, but I am not sure that people understand exactly what it is.

Marks To step back, I think it is important to understand that leukemia is basically another way of saying a cancer that affects the blood forming cells in the bone marrow. Just like there could be a breast cancer, which is of tissue of the breast, or a colon cancer of tissue of the colon, the bone marrow which produces blood cells is a tissue just like any other, and leukemia is a cancer that occurs in one of the cells in that tissue. It occurs from a cell that goes awry and then continues to divide when it should not. And normally that process of blood cell division is very well controlled, but when one particular cell loses its normal control mechanism, it keeps growing and growing and it essentially crowds out the normal tissue that would be there, the normal blood forming cells, and that creates many of the problems that we see in leukemia.

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Foss So fundamentally, all leukemias arise within the bone marrow?

Marks Pretty much so, there are rare presentations of leukemia where we see the major focus of leukemia outside of the bone marrow, but in general, they come up in the bone marrow.

Foss And you talked a little bit about patients developing fullness in their abdomen and a little bit about the symptoms of leukemias. Can you

tell us what other organs in the body are involved with leukemia? Marks In general, most patients with leukemia, when they come to medical attention, may notice that they have bruising on their skin or bleeding in their mouth. And sometimes patients will have frequent upper respiratory tract infections. Those are the types of things that we see in acute leukemias where people have symptoms. We tend to see fewer presentations of people complaining of large lymph nodes or swollen glands, and fewer presentations of people who are complaining of feeling abdominal fullness, which would be more common in the chronic leukemias. Foss We use the word acute to mean something that has happened very quickly. Can you give us an idea of how quickly acute leukemia can come on? Marks There is a spectrum of how fast acute leukemia can come on. We know from some people who have had normal blood counts a few weeks prior to coming to medical attention with leukemia, that at least in terms of the abnormalities in blood counts and symptoms it can come on in only a matter of 2 or 3 weeks. That does not mean that the first leukemic cell became apparent in the body then, but it means it's the first time anything measurable that we can see in the laboratory becomes noticeable. On the other hand, some people can actually take months to years to develop acute leukemia in certain settings, and there it is not truly acute, it is sub-acute, but that is a different story. Foss Peter, can you talk a little bit about the risk factors for leukemia? Marks In general, and I think this is a key message, for the majority of leukemias we still don't know what the causes are. There are certain things that do place one at increased risk for leukemia. Exposure to radiation is clearly a risk factor. We know that from people who have had exposure either to nuclear accidents or other scenarios. We also know that exposure to certain chemicals can cause acute leukemia, can be associated with it; also people who have had exposure to benzene or other organic compounds. And then increasingly, we understand that a certain population of people, those who receive certain6:24 into mp3 file <http://www.yalecancercenter.org/podcast/jan1710-acute-leukemias.mp3> chemotherapies for cancer, are at risk for therapy-related leukemias that occur because some of the treatments that we give can alter the blood-forming cells and lead to leukemia. Foss When you talk about radiation, there has been a lot in the newspapers recently about the medical use of radiation in terms of CAT scans and chest x-rays. Is that sufficient radiation to induce leukemia, and should the average person be worried about that? Marks To the best of my knowledge the amount of radiation during those diagnostic studies presented to individuals is not anything that really is of concern. If there is a good reason why someone is going to need a chest x-ray or CT scan, they should have it because the increased risk is really not noticeable in the scheme of things. Foss Thank you Peter. I think it is really important for our listeners to be able to put all that into perspective. Just a little bit more about the chemical exposure, a lot of people may or may not be exposed to chemicals at their work place, or potentially to chemicals in the home. To what degree do they really need to worry about that? Marks Today we are very lucky in that with increasing awareness there are various standards that have been placed on occupational exposures and home exposures of chemicals that

could potentially put one at risk for leukemia; many compounds we simply don't come in contact with the way we used to. Probably a good practice is to minimize your exposure to anything, but I think the chemicals that are really at the greatest risk have occupational exposures that are monitored and you cannot even get a hold of them at home.

Foss What about the genetics issue with leukemia? First of all, is it inherited? If somebody in your family has leukemia, do you need to worry about leukemia?

Marks That is a somewhat complicated question to answer, but I will try to answer it in a way that makes some sense of it. For a very large majority of people with leukemia, there is no genetic component that we are aware of, and that is probably 95 plus percent. There are a small number of patients who have leukemia where if you look back, they either have some family history of an increased frequency of leukemia, or they have certain genes that place them at increased risk of leukemia. But for the very large majority of people who have leukemia, we have no genetic basis that we can find, at least today, that is the cause of their leukemia. Another question that sometimes gets asked is, is leukemia transmissible from person to person in the home? If you have a person who has leukemia, can those cancer cells go from one person to another easily? And that is not something that happens.

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Foss What about the average age of patients with leukemia?

Marks Leukemia can happen across the entire age spectrum. Acute leukemias occur across the entire spectrum from children to very old adults. And in fact, most adults with acute leukemia, the most common acute leukemia which is acute myeloid leukemia, have a median age of onset of about 68 years. So the majority of people with acute myeloid leukemia will be over 65 years old.

Foss Is there any difference whether you get leukemia when you are younger or when you are older?

Marks There is, our ability to cure people successfully with acute leukemia really depends on the age of onset, and I will give you two extremes of this. With acute lymphoid leukemia, which is one type of leukemia that primarily effects children, we are now successful in curing more than 90% to 95% of the children who come down with this, when they are diagnosed in the age range of 4 to 8 years old. So we are very, very successful in that leukemia. At the other extreme, when we have acute myeloid leukemia, which is the common form in older individuals, if it is diagnosed in someone in their 70s, we probably cure less than 10% of those individuals. So it is a real big difference based on the type of leukemia and the age of the individual.

Foss So the approach for the individual patient then really depends on the number of different factors like their age and the subtype of leukemia that they have?

Marks That is correct.

Foss It is difficult when you think about the prognosis of leukemia, to really pinpoint one specific prognosis for everybody.

Marks That is absolutely correct. And increasingly we are finding broad prognostic categories based on age, based on types of leukemia, and also now, increasingly based on the molecular makeup of the leukemias.

Foss There has been a lot of research in leukemia recently, Peter, looking at those molecular subtypes and sub dividing patients, as you had mentioned, do

you feel that that is changing our approach to leukemia?11:48 into mp3 file <http://www.yalecancercenter.org/podcast/jan1710-acute-leukemias.mp3>Marks Yeah, more so than any drug that has been developed. I think the largest change over the past decade or two is not new drugs, it is that we have a better understanding of who is likely to do well, who we need to treat very aggressively, and who we can treat less aggressively. That has come from an understanding of the genetic composition of these various leukemias.Foss Can we take a step backward at this point and think about the individual patient who is diagnosed with leukemia? First of all, how do you make the diagnosis? What kind of work-up does that patient have? And what are the expectations for their treatment at the beginning?Marks The diagnosis is usually made after a patient has presented with some symptom that ultimately leads to a patient having a complete blood count. When that complete blood count is abnormal, one of two things can occur, either the complete blood count is very abnormal with a very high number of white blood cells, in which case the diagnosis can actually be made from just the blood count and work on the peripheral blood, that is blood taken from the arm or a vein, and we can make the diagnosis there. Or, when we have somebody who has low blood counts, or the blood counts are not very elevated, we sometimes have to do a test called a bone marrow examination where we take some of the bone marrow, a chip of bone, or some of the liquid bone from either the pelvis or some other location of the body in order to analyze it to make the diagnosis.Foss Peter, I would like to talk a little bit more about the treatment for leukemia when we come back after the break. You are listening to Yale Cancer Center Answers and we are here discussing treatment options for patients with the acute leukemia with Dr. Peter Marks.14:25 into mp3 file <http://www.yalecancercenter.org/podcast/jan1710-acute-leukemias.mp3>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. Peter Marks, an expert on leukemia from Yale Cancer Center. Peter, we talked a lot about who gets leukemia and how it is diagnosed, but can you tell us how we treat leukemia?Marks Treatment of leukemia depends on the type of leukemia that a patient has, and since we are talking about acute leukemias today, we would divide it up into the two major types of leukemias, acute myeloid leukemia and acute lymphoid leukemia. For younger individuals, people say less than 65 years of age, both of those are generally treated with systemic chemotherapy and usually a variety of different drugs that may be given over the course of a number of months. Sometimes these individuals even need to have a stem cell transplant. For other individuals, older people, and we said previously that people with acute myeloid leukemia tend to be older, sometimes we actually defer giving chemotherapy, or we will give very gentle chemotherapy and will mainly use supportive care measures, blood transfusion as needed, and antibiotics in order to support people through their illness.Chu The chemotherapy drugs that are used to treat acute myeloid leukemia versus acute lymphoblastic leukemia, the two most common acute leukemias, are they the same or different? Or perhaps they kind of complement

one another? Marks Some of the drugs overlap, but there is a different approach because acute myeloid leukemia is a disease that generally responds to one or two different drugs given over the course of several months that hopefully eliminates the disease entirely. On the other hand, acute lymphoid or acute lymphoblastic leukemias, actually require many different drugs to be given over a very long period of time on the order of years to eliminate it. There is one specific type of acute lymphoid leukemia, one that has a very specific genetic makeup. A quarter of people over the age of 60 will have a type of acute lymphoid leukemia in which there is a particular genetic abnormality that is a rearrangement of a gene called the BCR-ABL gene, which makes leukemia sensitive to an oral drug called imatinib, and in that case, we can't treat those individuals with that oral drug sometimes successfully for quite a number of years without ever having to give chemotherapy. Foss There is also a type of acute leukemia, a myeloid leukemia, which has a specific gene for which we have a specific therapy also. Marks That is right, and there is a particular type of leukemia that constitutes about 10% of acute myeloid leukemia called acute promyelocytic leukemia. That is a leukemia where we now understand that the administration of a particular drug called all-trans-retinoic acid dramatically improves our ability to cure the disease. It also dramatically reduces the number of people who die from complications of that disease. One of the real challenges in treating that disease previously was that it is a type of leukemia that is associated with activation of the coagulation system, so the people who presented with that would have tremendous amounts of bleeding, and they would often die before we could treat them from bleeding into their brain, or they would die as we treated them with bleeding into the brain, or otherwise. Now, with this particular treatment all-trans-retinoic acid, we give that before we give any chemotherapy and it seems to get rid of this bleeding tendency such that we have put a large majority of those people into long-term remissions, and in fact, that is a type of leukemia where, with current treatment, about 80 % of people are cured of their disease. Foss And that is basically a retinoid which is a derivative of vitamin A? Marks That's correct. Foss And another kind of leukemia, I guess, can be treated with arsenic, which is a drug that we have all heard of and is a toxin, but potentially also a therapeutic. Marks Right, it is actually that same leukemia, acute promyelocytic leukemia, and we also know that in that particular leukemia, the combination of all-trans-retinoic acid and arsenic trioxide can be used together for people who cannot otherwise take chemotherapy, and can lead to some very good complete responses and potentially cure. There is a good example of a 'targeted therapy', although some people might not consider arsenic their classic example of a targeted therapy, it does seem to work in patients with that particular leukemia to target the leukemia and eliminate it. Chu It is interesting that arsenic trioxide, and I think also all-trans-retinoic acids, were originally derived from Chinese herbal medicines. Foss That is right. Marks That is correct. These are both developments that came over to western medicine from China and the advances came through and were

adopted relatively quickly and it made a huge difference here adopting those medicines. Foss Peter, can you talk about the role of bone marrow transplant in leukemia? Marks Bone marrow transplant, some people get confused when we say bone marrow transplant and hematopoietic stem cell transplant, but we are going to use them interchangeably here, just 20:22 into mp3 file <http://www.yalecancercenter.org/podcast/jan1710-acute-leukemias.mp3> has to do with the source of where these cells come from, but bone marrow transplant, or hematopoietic stem cell transplant, has an integral place in the treatment of acute leukemias in adults. We use them to treat patients who have any type of poor risk feature that would lead them to be less likely to be cured by conventional chemotherapy. And unfortunately, the majority of adults who have acute leukemia, particularly myeloid leukemia, often have risk factors that make them do less than well. We tend to use it as a way to make sure that leukemia stays away for good. Without stem cell transplant or bone marrow transplant, we probably cure overall, in adults, a quarter to a third of people with acute myeloid leukemia. That number is doubled by having a population of patients go on to bone marrow transplant. Our age limit for bone marrow transplant now continues to get older and older, so that we actually have people who get reduced intensity types of bone marrow transplants into their 70s. Foss The important thing when you think about a transplant is that this is not actually a cure for the disease itself, this is a way to keep a patient in remission. Marks That is one of the ways to think about it. If you look at the number of people that are 5 years out of disease, which we quite often think of as cure, it is a way to make that happen. Chu Peter, you have been involved in treating patients with acute leukemias for quite sometime now. Looking at things in retrospect, what would you say have been the most significant advances over the past 5-10 years both in terms of, I guess, standard treatment options as well as the supportive care approach to these patients? Marks I think the largest advance, that I really appreciate, is that by understanding the genetic composition, leukemia is now at a better level than we ever have had before. And I think we are going to make very rapidly make more advances in the coming years. We understand who will benefit from our standard therapies, and who requires intensive therapy, and that will allow us to give patients the minimum amount of treatment they need to be long-term survivors. That way, we will not have people getting high-dose chemotherapy who don't need it, and people will go on to get high-dose chemotherapy that really need it because of these genetic factors that we are able to do. And that is one of the goals at a place like Smilow Cancer Hospital, the goal here is to increasingly be able to do personalized medicine so that we understand the actual genetic makeup of the leukemia, and then, address that with our therapy; that is one of the goals. Then another piece of it is that our supportive care has made huge advances over the past number of years. We are better in terms of our antibiotics. We have oral antifungal agents which we did not have a large number of previously that help 23:45 into mp3 file <http://www.yalecancercenter.org/podcast/jan1710-acute-leukemias.mp3> us to keep people's infections at bay, or prevent them entirely, so supportive care is

a large aspect of what we do. Foss There are also some monoclonal antibody therapies for leukemia. We talked about those in the context of other solid tumors and lymphoma. Can you talk a little bit about those? Marks The monoclonal antibody that probably is most relevant to acute myeloid leukemia is an antibody that is linked up to a toxin, so that the antibody kind of serves as a Trojan horse to get this killer molecule into the leukemia cells and that particular antibody, one of them is called gemtuzumab, is very useful, particularly in older patients, where it can be given in a manner to patients who could not tolerate other therapies safely. We are also increasingly using it in combination with other drugs as a way of salvaging patients, that is getting patients who have relapsed with their leukemia back into their remission. Foss Is there any role for radiation in the treatment of acute leukemia? Marks Occasionally there will be a role for radiation therapy. Sometimes people will have a mass of leukemic cells and radiation can be used to melt that away relatively quickly. In addition, sometimes people have leukemia that can just affect the skin, or mainly affect the skin, and there a special form of radiation therapy to the skin can be used. Chu Peter, you have been pretty actively involved in the past in terms of trying to develop new drugs for leukemias. Are there any interesting clinical trials that are available for patients? Marks We are increasingly developing a portfolio of trials that will involve various drugs. Right now we are kind of in between a number of trials but we are bringing more and more ones online and we are looking in particular to use drugs that are either standard drugs in novel combinations, or newer drugs that have less toxicity than some of their older counterparts. Aside from what we are trying to do here at Yale, patients can always go to the National Institutes of Health and the National Cancer Institute websites to look for clinical trials in their area. There are also support groups that are aware of clinical trials such as the Leukemia and Lymphoma Society. Foss You have done a lot of work in the hospital with older people with leukemia and you have developed some interesting combinations using new drugs such as histone deacetylase inhibitors and DNA methylation modulating agents. Can you talk a little bit about the role of those kinds of new therapies in older patients? Marks The treatment of leukemia in older patients takes into consideration many different factors. 27:02 into mp3 file <http://www.yalecancercenter.org/podcast/jan1710-acute-leukemias.mp3> It has to do not just with the patient's condition, but also what the patient's goals of therapy are. There are people who are 75 years old who have very different goals in life. Some people's goals may just be they want to have the next year or two and be able to see a major event happen, others have the attitude of they want to have 10 more years to go out and do many different things in their retirement. And so one has to take into consideration what somebody's goals are and with that in mind, one can take either a very minimalist approach, or one can use some of the regimens that we have tried to develop here using combinations of drugs that can be administered with modest toxicity, in other words regimens that can be given as an outpatient and tend not to require hospital admission. We combine drugs, for one example, a drug called decitabine which can be given as an outpatient

can be combined with the antibody we talked about before, gemtuzumab, and that allows us to administer therapy in the outpatient setting that is reasonably well tolerated. Chu Do older patients intrinsically have a different level of response to the drugs and the antibodies that you have talked about? Marks Well, we understand now that if you take the older population overall as a group, they clearly have a lower response rate to the drugs that we give. Going back to this discussion we had of molecular and personalized markers, it is clear that there are certain markers that seem to indicate that even an older individual will respond relatively well to a given therapy. As we understand this more and more, we may be able to pick out certain older individuals who we will treat with conventional therapies because we think that we will cure them and they will do very well over the long run, and then, the remainder of the population who we'll think about for other more novel treatments. Chu Peter, as always, it has been great having you on the show and we look forward to having you back on a future show to give us an update on the treatment and approach to patients with acute leukemias. Marks Thank you very much. Chu You are listening to Yale Cancer Center Answer and we would like to thank our guest Dr. Peter Marks for joining us this evening. Until next time, I am Ed Chu from Yale Cancer Center wishing you a safe and healthy week. 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 programs. I am Bruce Barber and you are listening to the WNPR health forum from Connecticut Public Radio.