Treatment of Leukemia

Guest Expert:
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Welcome to Yale Cancer Center Answers with Dr. Francine Foss and Dr. Lynn Wilson. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous 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 1-888-234-4YCC. This week, Francine and Lynn welcome Dr. Peter Marks. Dr. Marks is currently Associate Professor of Medicine and Hematology, and Director of the Leukemia Service at Yale-New Haven Hospital and Chief Clinical Officer of Smilow Cancer Hospital. Here is Francine Foss.

Foss  
Peter, the subject of our discussion today is leukemia, and leukemia is a scary word for everybody out there. I wonder if you could start by defining the word leukemia?

Marks  
Leukemia are a set of cancers that arise in the bone marrow from the cells that normally go on to form the cells of our blood. So, in a way, the analogy to this is it’s a tumor of the bone marrow and one of the cells of the bone marrow spills out into the blood.

Foss  
Can you tell us a little about how you got interested in leukemia?

Marks  
Getting interested in leukemia was a natural outgrowth for me of my interest in hematology, which is something I became interested in when I was doing my graduate work. I started a project where I was looking at white blood cells and how white blood cells of a body move and many of the cells that we looked at were cells that were derived from leukemia cell lines, and then after I completed my medical training it was a natural thing to go back to both studying more about leukemia and treating patients with leukemia.

Foss  
Can you talk about the age groups for leukemia, I know it occurs in children and even in older adults, could you talk a little bit about the distribution, how young and how old?

Marks  
There are two major types of leukemia. There is a type of leukemia called acute lymphoid leukemia and a type called acute myeloid leukemia. The difference is that one arises from a type of cell called lymphoid cells that normally go on to help form antibodies and help form immune defenses that circulate in the blood like antibodies, and the other type, called myeloid cells are cells of the body that normally help in immune defense, but they do it in a more direct way by eating invading organisms, and so the lymphoid leukemias are generally seen in younger people. Acute lymphoid leukemia is seen in younger people, whereas acute myeloid is seen in older people and so acute lymphoid leukemia is something that we see with a peak age of around four to eight years old, whereas acute myeloid leukemia occurs across the age range, but particularly starts to increase in incidence as people get into their 60s and 70s and the median age of onset is about 68 years of age. The chronic leukemias, and there is a chronic counterpart to each of the acute
leukemias and we can talk about the difference between acute and chronic in a minute, but the chronic leukemias include chronic lymphoid leukemia, which is primarily a disease of older people, again with an incidence where the average age that people develop it is in their 60s and chronic myeloid leukemia can also occur across the entire age spectrum, but tends to occur in people in middle to late middle age, usually in their 50s or so.

Foss How do most patients with leukemia present?

Marks It would depend on whether they have an acute or a chronic leukemia. Let’s start with an acute leukemia. Acute leukemia’s tend to present related to a deficiency in one of the three major blood cell types. The red blood cells, the white blood cells, or the cell that is involved in blood clotting called the platelet, and so if you have presentation of acute leukemia sometimes people will present with recurrent infections or fevers and that is because of a deficiency in the white blood cells or because they have too many white blood cells that are not functioning right. They can present with shortness of breath because of having anemia, low red blood cells, and they can present with bleeding complications because they do not clot or they bruise easily because they have low blood platelets, or they can have a combination of any of those things. So, that is how acute leukemia tends to present and sometimes, less commonly, it is something that is found on a routine laboratory test done by a provider. In contrast, the chronic leukemias are actually more often than not today found almost incidentally when somebody does a blood count. So, somebody goes to their doctor and will have blood counts done as a part of a routine physical or because of some unrelated complaint and the doctor notices that the white blood cell count is high and that either there are too many of the lymphoid cells or too many of the myeloid cells present and that subsequently leads to the diagnosis. When people do present with symptoms of chronic leukemia it tends to be things like swollen lymph nodes, or in the case of chronic myeloid leukemia, it can be with an enlarged spleen, so sometimes people develop early satiety, so they feel full more quickly than usual when they are eating or they notice the sensation of fullness on their left side.

Foss So many patients with chronic leukemia feel fairly well when they go to the doctor?

Marks That is correct, and it is interesting that you brought up the word scary to describe leukemia. People who have an early form of one of the chronic lymphoid leukemia’s, often will go many-many-many years before ever needing treatment, so they feel fine and they do not note that they have anything and so the funny thing is that you tell them they have this thing, this chronic leukemia, and it is a terribly scary thing and yet it won’t affect their lives for many years to come. So it does present a little bit of a challenge in that regard.

Foss Peter, a lot of people will go to the doctor and there might be some abnormalities in the white blood count and people may be worried about leukemia. Could you talk a little about the risk factors for leukemia and when you actually have to worry and what the other things are that could cause an elevation in the white count?

7:24 into mp3 file [http://yalecancercenter.org/podcasts/2012_0115_YCC_Answers - Dr_Marks.mp3](http://yalecancercenter.org/podcasts/2012_0115_YCC_Answers - Dr_Marks.mp3)
Let’s start with the risk factors for leukemia. To a large extent we do not understand the risk factors that cause leukemia, but there are certain specific things. For instance, for acute myeloid leukemia, we know that radiation exposure and exposure to certain chemicals, benzene and certain organic chemicals is associated with significantly increased risk of leukemia. In addition, some people had chemotherapy in the past for other diseases and are at a higher risk of having leukemia, plus there are certain diseases. Diseases like myelodysplastic syndrome or myeloproliferative syndrome which can turn into acute myeloid leukemia. So those are the things that can be preconditions that can be associated with it. When people turn up with a high white blood cell count, the most common thing is that they have some type of infection or some type of stressor to their system that is leading to that, so the first thing to worry about with the high white blood cell count is generally not a leukemia, that is the first thing to remember, that oftentimes it could be an infection or an inflammatory condition, and so when a white blood cell count is elevated, it is very important to understand what types of white blood cells are elevated.

Can you talk a little bit about how we actually make the diagnosis of leukemia?

The most common ways that we make it, are one of two ways. If there are a sufficient number of circulating white blood cells that are abnormal we are able to do a test called flow cytometry on the blood that is drawn from a vein. That is a test in which the cells are stained with these fluorescently labeled antibodies. This is a technique which allows us to do determine in the blood the different types of white blood cells with great specificity and it allows us to understand if there is one particular type of white blood cell that is standing out in excess. The other way we sometimes need to make a diagnosis is to do something called a bone marrow examination in which case, we take a little bit of bone marrow from the back of the pelvis and then look at it under the microscope and process it by similar techniques to that which we do with the blood such as flow cytometry and other tests and that allows us to get a definitive diagnosis of whether leukemia is present or absent.

With most other cancers we talk about getting scans like MRIs and PET scans, is this part of your evaluation for leukemia?

It would depend on the type of leukemia, and also depends on the type of presentation. So for the acute leukemias, we generally do not need to get scans because most of time we are talking about a problem that is related to the bone marrow. There are a few exceptions to that but I would not delve into them here. On the other hand, for the chronic leukemias, particularly for chronic lymphoid leukemia, we would tend to think about getting scans particularly if somebody presents on their physical examination with enlarged lymph nodes or if their spleen is something we can feel on examination, or if they have a particularly high white blood cell count. So, scans in leukemia are mainly reserved for following up physical findings when we examine patients.
Once the patient has a diagnosis of leukemia, can you take us through what the next steps would be, say, say for acute leukemia?

It is very important to feel comfortable with the person who is treating you when you have leukemia because this is a relationship that you are going to have with someone for quite some time. For acute leukemia, the treatment courses are generally on the order of 6 to 12 months and that’s if somebody has an uncomplicated course and it can go on for much longer so you want to establish a good relationship at a center that you trust, and once you have that, the next step is usually to be admitted to the hospital to undergo something called induction chemotherapy. What we mean by induction chemotherapy is that it is a process whereby we give some form of chemotherapy or combination of chemotherapy drugs that eliminate the leukemia from the bone marrow in terms of the amount of gross disease that is present. It doesn’t mean cure but what it means is getting rid of the majority, the large bulk of the leukemia, and that usually takes three or four weeks in the hospital and from there, one uses a variety of different strategies which really depend on the type of acute leukemia to keep the leukemia away, and sometimes it ultimately requires a hematopoietic stem cell transplant, also known as a bone marrow transplant.

During the course of the hospitalization for acute leukemia, can you talk about how sick patients are and do they go back to work in between their treatments, or is this really a six month to a year process where they are out of their normal life?

In general, when we are treating patients for acute leukemia it really does mean that the patients need to take a break from their general work activities. There are some patients who can do some work, if they do light work such as computer programming or that type of thing, but in general, patients need to take a break out of their lives for treatment and I think that is wise because there is enough stress with the chemotherapy and all the different things that people are going through, plus most people react differently, one person will react differently to the chemotherapy than another and one cannot always predict, so it is probably wise in general, when someone is diagnosed with acute leukemia, to plan on being out of work for several months while you are getting chemotherapy.

We are going to take a short break now for a medical minute. Please stay tuned to learn more about the new developments in leukemia with Dr. Peter Marks.

There are over 12 million cancer survivors in the United States right now, and the numbers keep growing. Completing treatment for cancer is a very exciting milestone but cancer and its treatment can be a life changing experience. Return to normal activities and relationships may be difficult and cancer survivors face other long term side effects of cancer 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 one at Yale Cancer Center to keep cancer.
Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined today by my guest Dr. Peter Marks and we are discussing new developments in leukemia. Prior to the break, Peter, we talked a little bit about acute leukemia and the treatment course for that. Can you update us a little bit about chronic leukemia? How are patients treated? How long does it take and what are the outcomes for those patients?

Peter We can talk about the two different leukemias, chronic lymphoid leukemia and chronic myeloid leukemia and the treatments for them are very different. Chronic lymphoid leukemia, for many of the patients that are diagnosed with it, is treated with what we call watchful waiting, which is basically having checks of the blood counts at intervals, usually every three to six months, physical examinations, and maybe an occasional scan, but we really just watch it because we know that when somebody has only an elevated white blood cell count and no other evidence of the disease, it can be 10 or even 15 years on average before they will need some type of treatment. So really that’s a matter of remaining with the patient, reassuring them that we are watching things and we are actively watching things and that nothing actually needs to be done in terms of an intervention. When we do need to treat chronic lymphoid leukemia, we can treat it with a variety of different drugs and what we treat it with will depend on how old someone is. If somebody is a younger patient we will treat it relatively aggressively with an attempt to get a complete remission sometimes with the hopes of ultimately taking them to a stem cell transplant, as we said before, also known as a bone marrow transplant. For older individuals we are generally trying to make the disease better without actually trying to cure it and so we will use a combination of somewhat gentler chemotherapies and will go from one set of agents to another, so patients, although they may receive one set of chemotherapy drugs, we now have many different drugs, so we can use one drug and then it will work, or one drug combination, and then it will work for some time, and if the leukemia comes back, we will use some other drug. For chronic myeloid leukemia it’s a very different story, because here is one of the real triumphs in science and medicine over the past two decades. Chronic myeloid leukemia is defined by the molecular genetics of the disease, there is a very specific abnormality that occurs in the chromosomes where there is a kind of reconnection of two genes which leads to a switch being turned on in the leukemia cells and that switch is necessary and sufficient to cause the disease. So once we understood that, and that understanding took place over two to three decades, but once that was understood, about a decade ago, an agent was introduced into clinical use which essentially blocks that switch from functioning and kills off the leukemia cells in a large majority of the patients treated, and that’s a drug called imatinib and it is one of those drugs called a targeted therapy, because it specifically acts in this type of leukemia, and in a few other diseases, to turn off the cancer, and about 90% of people treated with it, will go into at least hematological remission, and some, 30% or 40%, will go into extremely good
remissions with almost disappearance of the disease, it is quite impressive that a disease that was uniformly fatal 40 years ago, chronic myeloleukemia without a stem cell transplant, would have been a fatal disease pretty uniformly and today it is a disease treated usually with a pill once or twice daily.

Foss Would you go so far as to say that we are curing patients with chronic myelogenous leukemia?

Peter Yes, sometimes it is debated because there are people that would say chronic myeloid leukemia or chronic myelogenous leukemia are the same disease, just a different terminology is used to describe it. With imatinib there is a population of patient’s who after they are treated have disappearance of even molecular evidence of disease from their blood, they actually appear to be cured because when you take them off the drug they do not appear to have recurrence. Now we are a little bit hesitant to say that for sure because we only have data now extending for a few years, but the hope is we are potentially getting towards cure for that. We do not know for sure yet, but in any case even if we are not showing it, we know that for patients treated with imatinib for 10 years they remain in remission and for patients who have had very good remissions with imatinib they do not seem to progress on to more advanced stages of the disease.

Foss What is the quality of life like for one of those patients on a drug like imatinib for a long period of time?

Peter Drugs like imatinib, all of them have some side effects, but in the majority of patients, I would say maybe 75% of patients, people tolerate these drugs remarkably well. When they are started on them, they might notice a little fluid retention or some rash, some people even have some joint aches, and those things usually resolve with time. There are some patients, and it depends on the drug and the situation, but some patients do have side effects, and drugs need to be switched to alternatives and thankfully alternatives exist. Some of the things that can cause problems are that people can get constant nausea, or they get very severe skin rash and some people have problems with their blood counts and those will be reasons why one would need to switch to a different drug.

Foss It sounds like we have made some tremendous success here. I wonder if you could just talk in general about your experience over the years with acute leukemias and whether you feel that we have made any major advances in the treatment for those patients with the more acute form of the disease?

Peter For acute leukemia, it is really a sobering thing to understand that our advances have not had to do so much with new drugs, but they have had to do with our molecular genetic understanding of the disease and how we now understand who we should treat aggressively, and who we should take a less aggressive approach with because we may not be curing them and by giving them very toxic chemotherapies, if anything, we are shortening their lives rather than helping them. Molecular
genetics today has remarkably altered how we think about treating people, particularly in older individuals. For example, we now understand that if somebody is 70 years old and presents with acute leukemia, there are a variety of ways that one could potentially treat them if somebody has a very good performance status, one can take a very aggressive approach in treating them, particularly if they have certain molecular genetic mutations associated with a very good outcome. It turns out that there is a particular gene, one of them is called the nuclear folsom1 gene which when it is mutated in an older person, is associated with a very good outcome when we treat those individuals with the standard types of chemotherapy that we use for treating younger individuals. On the other hand, there are some molecular genetic abnormalities that when present in an older individual really auger for a very poor prognosis and regardless of what we treat those individuals with, they are not likely to have long term survival without some type of investigational therapy or something like a stem cell transplant.

Foss Is it standard of care now to be looking for these specific genes in all our patients who present with leukemia?

Peter I would say that it is absolutely standard of care to make sure that what we call cytogenetics, we look at the chromosomes that are in the leukemia cells, that is absolutely standard of care today and I would like to think that in academic centers it is becoming pretty routine standard of care to look at a panel of molecular genetic tests to understand whether someone has positive or negative prognostic features. The exact tests that are in that panel are going to vary from place to place because it is an evolution, but I think certainly looking at the chromosome content of the leukemia cells and looking at a few molecular markers is becoming pretty standard.

Foss Peter, we have talked on the show in the context of other cancers about identifying mutated genes and developing specific therapies and we certainly have imatinib in CML, I am wondering with some of these new mutations that we’re identifying, is there an effort underway to develop some targeted approaches for some of these specific disorders?

Peter That is absolutely the case in leukemia and in acute myeloid leukemia there are several different clinical trials going on looking at drugs that have not yet been approved for prescription by a doctor. So, the clinical trials are looking at particular targets that have been identified, one of them is a gene called FLT3 and that is a gene that is abnormal in certain types and certain percentage of acute myeloid leukemias and there are several different drugs that target that abnormality and we are hopeful that by targeting that abnormality, in addition, perhaps to giving other chemotherapies, we will lead to higher rates of cure when that particular gene is mutated.

Foss Are there any new biological therapies for cancer? I know at one point we had a monoclonal antibody therapy and I am wondering are there other such therapies?

Peter Monoclonal antibodies are used in the treatment of chronic leukemia. In terms of chronic lymphoid leukemia, there is a monoclonal antibody that is very commonly used when patients
need to be treated called rituximab. It actually attacks leukemia cells because of a marker that is present on their surface and it does so very well and it can be used repeatedly over the course of time. For acute myeloid leukemia there are antibodies that have been in development that attack those cells as well, and actually at our recent American Society of Hematology Meeting, which was held in the beginning of December, there was some evidence that when one of those antibodies, which is conjugated to a toxin is used, it seems to actually improve survival in patients with acute myeloid leukemia. So, I think we are seeing advances there in terms of these biologic therapies, either antibodies alone, or antibodies that can be linked to either some type of toxin that kills the leukemia cells or even to radioactive molecules that can help kill the leukemia cells.

Foss Peter, if you undergo treatment for leukemia and then you relapse, is there hope at that point? What are new approaches that are being used in that situation?

Peter Again, here we are able to divide into chronic and acute. Let me take chronic first, for chronic lymphoid leukemia, if one relapses it is basically expected unless someone has a transplant. So, we are used to that and we go from one chemotherapy regimen to another. For chronic myeloid leukemia, if somebody progresses through their treatment, we now have a variety of these different specifically targeted therapies that we can move from one to another and we can actually even look at what type of mutation is present in order to best target that particular mutation and sometimes, ultimately in the chronic myeloid leukemia situation, we might move towards a stem cell transplant, bone marrow transplant. For the acute leukemias, when patients relapse the hope is that we will salvage those, be it acute myeloid or acute lymphoid leukemia, with a chemotherapy regimen and then ultimately in that situation when somebody has a relapse, we almost always move towards stem cell transplant when we have a donor available. That is because in that setting when an acute leukemia has relapsed, it is telling us that we have a very serious disease on our hands, which is not likely to be cured by conventional therapy. There are a few exceptions, there are specific types of acute leukemia called acute promyelocytic leukemia where relapse could potentially be treated with conventional chemotherapy and lead to cure but that is a very specific type of leukemia which is actually treated with specifically targeted therapies. The rest of the leukemias when they relapse we are generally thinking about moving towards transplant.

Dr. Peter Marks is currently Associate Professor of Medicine in Hematology, Director of the Leukemia Service at Yale-New Haven Hospital and Chief Clinical Officer of Smilow Cancer Hospital. If you have questions or would like add your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.