Living with a Chronic Leukemia Diagnosis

Guest Expert:
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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 welcomes Dr. Peter Marks. Dr. Marks is an Associate Professor of Hematology at the Yale School of Medicine, Chief Clinical Officer at Smilow Cancer Hospital, and an expert in the treatment of leukemia. Here is Ed Chu.

Chu Peter, perhaps you could start off by giving us a brief overview of the different types of leukemias.

Marks Leukemias are basically cancers of the blood in which a cell goes awry and starts multiplying, essentially out of control. The chronic leukemias are distinguished from the acute leukemias in terms of the mature counterpart that they represent versus the immature counterpart, which is the acute leukemia. Acute leukemias originate from cells that are like immature cells, whereas the chronic leukemias originate from cells that look very much like normal mature blood cells, but they have some subtle difference that lead them to keep going on and on and making more and more of themselves, unlike normal blood cells that actually stop and regulate themselves at any given point. In a way, one can think about acute leukemias as a disregulated process, that is why they are acute, they come on very suddenly or relatively rapidly. The chronic leukemias often times look somewhat like normal cells, they behave somewhat like their normal counterparts, but they just grow and grow and grow in number and eventually cause problems over time.

Chu How do you as a hematologist, and a specialist in hema-malignancies, determine whether or not you are dealing with an acute leukemia versus a chronic leukemia?

Marks The distinction between acute leukemias and chronic leukemias has to do sometimes with the types of cells we see circulating in the blood, and often times it is as simple as obtaining a blood smear and a complete blood count from the patient. Other times it is more complicated and it requires a bone marrow examination taking a small amount of bone marrow from either the pelvis or another location of the body and looking at that under the microscope with special techniques that characterize the types of cells that are there.

Chu Is there any difference with respect to say the age group in which acute versus chronic leukemias are present?

Marks Acute leukemias can occur across the entire age spectrum, and in fact, certain leukemias like acute lymphoid or acute lymphoblastic leukemia are more common in younger individuals,
even children, whereas acute myeloid leukemia is more common in older adults. The chronic leukemias tend to occur in middle age, although chronic myeloid, or chronic myelogenous leukemia, can occur across the age spectrum. Chronic lymphoid leukemia, on the other hand, tends to occur in adults or older adults. That is the one where we really don’t have a pediatric patient population.

Chu You just mentioned chronic lymphocytic leukemia. Why don’t we go ahead and start focusing on the chronic leukemias, CLL as it is also known?

Marks I will probably launch into calling it CLL rather than chronic lymphoid, or chronic lymphocytic leukemia. CLL is a disorder of the immune cells that normally go on to help in the production of antibodies, and antibodies help protect us from infections. There is a cell type that is involved in their production, or that goes on to mature into a cell that can help with the antibody production, and that is the cell that is involved in chronic lymphoid leukemia. What happens is it is a relatively normal-looking cell when we look at it in the blood smear, but it has certain abnormal properties that allow us to distinguish it in the laboratory. Instead of stopping at a certain number of cells, it continues to grow and grow and accumulate in numbers until it causes problems. It can cause problems either by having very high numbers of cells in the blood, or because it can take up residence in certain tissues of the body such as lymph nodes and cause enlargement, or another tissue the spleen, and cause enlargement of the spleen and that can cause issues for patients. Also so much of it can be present in the bone marrow that it displaces the normal bone marrow cells, the normal red blood cell, white blood cell, precursors, and then you can get anemia or low blood platelets. Blood platelets are involved in clotting and those things can get low too in this disorder.

Chu Can you review some of the symptoms that are typically associated with this disease?

Marks The most common presentation of chronic lymphoid leukemia is no presentation. Most commonly the person goes to their doctor and the automated counters that do our complete blood counts, they are so good that they pick it up, there is a little elevation or modest elevation in the white blood cell count, and then the doctor calls the patient back and additional tests are done, ultimately leading to a diagnosis. Many patients have no symptoms whatsoever. When patients do have symptoms, they tend to be enlarged lymph nodes, they might notice them in their neck, a lump a marble or two marbles in size, or they might notice multiple marbles. Sometimes if people have large spleens, they might notice fullness in the left side of their abdomen and those would be symptoms of the cells essentially infiltrating the normal tissues of the body.

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All of us at some time or another will have marbles, or lumps, or bumps. How do you distinguish between the normal type of lymph node enlargement and say the lymph nodes enlarged because of CLL?

This can be tricky at times. A good rule of thumb is if something is the size of a dime or smaller and there are just one or two of them, usually that is normal. All of us when we get a cold, a virus, a dental infection, can get a few small enlarged lymph nodes in our neck, and in fact, it is normal to have some enlarged lymph nodes in the groin that are that size or even a little larger. If one were to notice multiple lymph nodes, particularly if they start to be the size of a quarter or larger, then one starts to think about could this be something. Although it may be nothing, it is probably worthwhile to seek medical attention if there are multiple nodes that are getting towards the size of about a quarter, probably 1 cm or 2 cm, or about $\frac{1}{2}$ inch to an inch in diameter.

What do we know about the risk factors for CLL?

We don’t know a tremendous amount, I wish we knew more. There are probably some exposures that might increase this. We do know that there is probably some genetic component because there are some rare families, not a common thing, but there are some rare families that seem to have a heightened incidence of CLL, but by and large, it happens in people who really don’t have any risk factor for it that we can tell.

Once the diagnosis of CLL is made, what is the general treatment approach for those individuals?

The treatment approach really depends on what stage it is diagnosed and we diagnose it and then categorize it into one of essentially four stages. The most common one that we have in our clinics is people who require no treatment and they are considered at a stage where we believe the treatment is watchful waiting, and many people go years without ever needing to have any type of treatment; we just follow them along. Sometimes, initially we might follow them along every three to six months, and then, if they are very stable, we let that spread out to longer intervals. There are quite a number of people whom we just follow along and make sure that nothing is going on. Then there are people who have enlarged lymph nodes that start to bother them or they have low blood counts and those people require treatment with some type of medication.

And that type of medication, is it chemotherapy? I know there is a lot of talk about using targeted therapy, or a combination of chemotherapy and targeted therapy, what are your thoughts on how to treat these folks?

Generally we decide upon a treatment based on a person’s age and how well they are doing overall. Somebody who is a younger person, say under the age of 60 or 65, who is active, we tend to treat relatively aggressively with a combination of chemotherapy and a biologic therapy. When I say a biologic therapy, what I am talking about is a monoclonal antibody, an antibody that can recognize this particular cell type that is involved in CLL and help to eliminate it. In some cases you can use this drug alone, but in a younger person we tend to be very aggressive, and we will treat with a combination, usually two chemotherapy drugs, one called fludarabine and another one called cyclophosphamide, and we will add on to this monoclonal antibody to one of the cell surface determinants called rituximab and that combination has recently been approved, actually just last week, for the treatment of chronic lymphoid leukemia.

And are there any side effects associated with either the chemotherapy or this rituximab biologic therapy?

The chemotherapy certainly has potential side effects. It can drop the blood counts significantly, and that puts patients at risk for bacterial infections. It also is an immunosuppressant and that can lead to viral infections or viral reactivations. So, when we prescribe the chemotherapy, we are also cautious to give appropriate prophylactic medicines, antibiotics or antiviral agents that help to prevent these other complications from occurring, essentially forearmed against these complications.

With these treatments, can we cure patients with CLL?

In general, we don’t cure patients with CLL. The only curative therapy that we really have today is doing stem cell transplantation. That being said, for many patients, we put them into remission for reasonably long periods of time and then we go from one therapy to another over the course of time, so it becomes more of a chronic problem than an acute one. They might require re-treatment every several years with some different combinations. Now, as the years have gone by, we have more and more different drugs for CLL, so we are hoping that this will become more and more of a chronic thing that even if we cannot cure it, we can go from one therapy to another hopefully with the minimal toxicity possible.

That is the important point to emphasize to our listeners about this disease; one can live with this disease for a long period of time and do extraordinarily well.

That is correct, and what we are also able to do now is identify, using molecular markers and cell surface markers, people who are at higher risk of having early progression, and those are people that we might be more aggressive with, or we might use an alternative treatment with,
because by no means the majority, but a fraction of people will have a risk factor that will make us suspicious that they may go on to have problems more quickly, and we may be more aggressive with those individuals. Over the course of the next year, as we see more and more trials getting more and more personalized looking at the nature of the CLL and trying to address the disease itself, some people we may see it and will say look, now we understand, you are not likely to get into problems with this for many years, and with others we will say, you have some features here that say things are growing, you are already having problems, we should be more aggressive with this. I think we will see that happen over the next years.

Chu: Why don’t we go ahead and take a short break for a medical minute. We are here in the studio this evening with Dr. Peter Marks who is an expert in the treatment of acute and chronic leukemias. Our topic for this evening’s show is the treatment and approach to patients with chronic leukemias.

Medical Minute: Here in Connecticut, the American Cancer Society estimates that almost 1000 people will be diagnosed with colorectal cancer every month. The good news is that when detected early, colorectal cancer is easily treated and highly curable. That means that if you are over the age of 50, you should have regular colonoscopies to screen for this disease. In the case of patients that do develop colorectal cancer, there are more options than ever before, thanks to increased access to advanced therapies and specialized care. Clinical trials are currently under way at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for colorectal cancer. Patients enrolled in these trials are given access to medicines not yet approved by the Food and Drug Administration. This has been a medical minute and you will find more information at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting network.

Chu: Welcome back to Yale Cancer Center Answers. This is Dr. Ed Chu and I am joined here in the studio with my good friend and colleague Dr. Peter Marks to discuss the diagnosis and treatment of chronic leukemias. Before the break we were discussing chronic lymphocytic leukemia, also known as CLL, and I think we probably should now turn to the other chronic leukemia which is known as chronic myelogenous leukemia, or CML. Can you give us a little bit of background information on CML?

Marks: Chronic myeloid leukemia is a leukemia with the peripheral blood in our blood streams and what happens is it looks like the bone marrow has decided to take up residence in the blood stream and the blood counts get higher and higher with cells that look basically normal. The cells look normal for their counterparts in the blood or for counterparts that would normally be in the bone marrow, but eventually what happens is that the disease over the course of
time, pretty reproducibly after several years if untreated, turns into an acute leukemia, and either an acute myelogenous leukemia or an acute lymphoid leukemia. It can go either way, but initially for the first several years it is a disease in which it is mature and immature blood cells that circulate and are not that abnormal looking, but you have way too many of these cells in the blood.

Chu And again is there a certain age group in which you typically will see CML present?

Marks It tends to present in middle aged to older individuals, but it can occur across the entire age spectrum.

Chu And with respect to risk factors, what do we know about?

Marks Not a whole lot. We know that probably certain exposure to certain agents may slightly increase the risk of CML, and we think there might be some issues with radiation exposure, but again, the large majority of people who get CML, we really don’t find one of these, and so we are still left without a good explanation for the majority of cases of CML that we see.

Chu Is there any kind of genetic component to CML?

Marks To our knowledge, there is isn’t, I should say, there isn’t an inheritable component. There is nothing passed on really from parent to child. On the other hand, we know very well that this is one of the leukemias that is defined by a genetic abnormality just in the blood, so it is important when we talk about this as we are going to talk probably in the next couple of minutes, about a genetic abnormality in CML. What we are talking about is a genetic abnormality that is confined to the patient’s blood cells; it is not something that they can pass on to their children.

Chu Again, let us talk about how you make the diagnosis of CML?

Marks CML is usually found because somebody presents with a high white blood cell count, and there are usually immature forms present on the blood smear. These are forms of blood cells that would normally only be found in the bone marrow, but instead they are found in the person’s blood, and once we see that, probably the simplest way to make the diagnosis quickly is to use molecular testing. We send the test off which looks for the specific molecular abnormality called the BCR-ABL translocation, these are two genes that normally are far apart, one is located on one of the chromosomes, chromosome 9, and the other is located on another chromosome, chromosome 22, and they get put next to each other and what happens is that one of these genes that is normally very active in regulating a multitude
of cell processes, is no longer regulated, and the switch gets switched on and switching that switch on is necessary and sufficient to cause this disease. There is some elegant scientific work that has been done in mice to show that all you need to do is take this one abnormality, put it into the mice, and out comes the picture of CML. That actually has helped us in learning how to treat this disease because we now have models that can allow us to develop therapies.

Chu: There are no normal cells that have this molecular abnormality?

Marks: This is not one that is just an innocent bystander, at least to the best of my knowledge.

Chu: How quickly can that molecular test be done to actually determine whether or not an individual has CML?

Marks: The molecular test can be done within a matter of hours. The largest thing is mainly the turnaround time of getting the blood processed. The other way that the diagnosis can be made is by standard analysis of chromosomes and that can be done either on peripheral blood or on a bone marrow sample, or by a special test on the chromosomes called fluorescence in situ hybridization. That can be done overnight, essentially. Really the diagnosis can be made in most cases by one or the other means, really overnight, once a sample is obtained.

Chu: When you, as a leukemia expert, have a patient who has been given the diagnosis of CML, what is the thought process in terms of different treatment approaches?

Marks: The thing that I love about CML is when I see a patient who has been given the diagnosis, I feel relief because even though you may see on websites and in literature, tremendous talk about issues with resistance to therapies, etc., this is one of the cancers that I wish we could mirror in our treatment of other cancers, because we have a specific molecular abnormality and because of that, we were able to develop, with time as a science, certain individuals we’re able to develop therapies which target this particular abnormality. A drug was developed initially called imatinib, and that drug targets this, it targets several others as well but this particular genetic abnormality in these blood cells, and when given to patients it is well tolerated and essentially eliminates the evidence of the disease, it makes people have hematologic remission, in other words, you don’t see any evidence of it in the blood. It can also make people have no evidence of it in their chromosomes in their blood cells, and using sensitive molecular techniques, it can even make people have no evidence of it by those techniques, so it is a very powerful drug that is able to put probably about 90% of people who take it into very good remission. We now know from about 10 years of experience that people stay in remission once they get into remission. Not every person does but a
significant percentage, 85% to 90%, of people who achieve remission, stay in remission. It is a very effective agent and I wish, not that I wish anyone to have CML, but when people come, it is a relief to be able to tell people that they have a disorder that we actually have a pill for that can put them into long-term remission.

Chu What is really remarkable is that before this drug was made available, we really couldn’t cure patients with CML.

Marks When I started my training there was no imatinib, and what we did for younger people, people younger than 50 or so years of age, was we took them to bone marrow transplants because we knew, and as I started out saying, it was very reproducible. If you didn’t do anything about the disease, after 3 or 4 years of treatment with something to just hold the white count at bay, people would develop a leukemia that was so bad that no treatment would cure it. We would take people to stem cell transplants or bone marrow transplants to prevent that from happening, and unfortunately, the good part is we probably cured a fair number of people that way, but the downside was that we took people who were very healthy and we lost a fair percentage of patients with toxicities from the transplant or from other complications of transplant afterwards.

Chu Are there any side effects associated with imatinib?

Marks Imatinib is most commonly associated, the most common thing that people have, and it usually goes away with time, is some fluid retention that can occur with it; fluid retention sometimes in the lower extremities near the ankles for reasons that are not entirely clear, sometimes it occurs around the eyes and that usually goes away with time. In addition, some people develop rash to the drug or they can develop low blood counts due to the drug that persist over time. Low blood counts, initially, on the drug are very common, that is because as the bad cells are wiped out, there is a period where it takes good ones to grow. On the other hand, some people after several months on the drug, still have low blood counts, and then alternatives need to be considered, which exist.

Chu As you mentioned, resistance can be an issue in some patients, so if someone should develop resistance to imatinib, and for listeners out there this drug is also known as Gleevec, what are the treatment options in that setting?

Marks We now have at least two other drugs and there are others in development. These are two licensed drugs, but there are others also in development that are there to address resistance that can develop. Resistance happens when the protein that is produced, the gene actually codes for things that prevent the drug from binding to it, along with other mechanisms.

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of resistance that can occur. By giving these other drugs, we can overcome that. There are
two different ones that we use, and their side effect profile is also somewhat similar. It is
again slightly different to imatinib, but a fairly high percentage of those patients we get into
remissions using those drugs. There were a small percentage of patients who have particular
mutation that doesn’t respond to any of the currently licensed drugs, but there are clinical
trials of agents ongoing now to try to address that particular abnormality, that particular
mutation.

Chu You mentioned awhile ago that there are some patients who can go from having the chronic
form of the disease to it becoming acute leukemia. Are there molecular tests that can help us
to identify who is going to transform into a more acute form?

Marks We know that more abnormalities besides the BCR-ABL translocations in the chromosomes
of cells, probably are not a good thing, especially if there are a lot of early cells, what we call
blast cells in the bone marrow. On the other hand, probably the most useful thing we have
today for following patients over time is the ability to follow patients with a molecular
diagnostic test, which is quantitative. So, we can look at patients’ blood over the course of
time, usually we do it about every three months in people on imatinib, and see how well we
are clearing this transcript, this protein essentially, and we like to see that we have none of it,
but even if we don’t achieve that, as long as we have achieved significant inroads on getting
to nothing, that is usually a significant advance. Many people who don’t achieve complete
absence of the protein have very long remissions even though we can detect some of it with
the molecular test.

Chu If in fact we get the more aggressive acute forms, what would be the treatment approach in
that setting?

Marks That actually depends on how someone has gotten there. In some cases, in these more acute
forms, we will actually try one of the other oral agents alone and see if it actually gets
somebody into remission, because it is probably about a third of people who get a different
one of these drugs, if they were on imatinib they might get dasatinib or nilotinib, two of the
other agents, and they will go into remission. They will not stay in remission for long, so it
means we have to do something else like a stem cell transplant afterwards, but it is a way of
getting people into remission without having to give them conventional chemotherapy.
There are people who have very high white blood cell counts that have to be treated, we have
to give conventional chemotherapy to, and that means putting people, most of the time, in the
hospital and then giving standard chemotherapy drugs that have the toxicity associated with
them.

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Chu  It is interesting that the development of imatinib/Gleevec, which really I think has served as the poster child for targeted therapy, made everyone try to focus on identifying that key molecular target that you can then use to identify new therapies. What are your thoughts on that?

Marks  It is interesting because some people will get very upset with us when we talk about imatinib and how it is this wonderful paradigm, because they say other cancers are so much more complex, but I would view this as a wonderful reductionist approach where we can do it here and now we can hopefully export this. It may be more complicated as we look at other cancers, so when we look at colon cancer, it may be that it is not just one tyrosine kinase, it may be several different genes we need to address with specific molecules, but the hope would be that eventually, by coming up perhaps with a soup, or a Chinese herbalist approach of a combination of different medicines, we might be able to address cancers that are otherwise much more complicated. In a way, by being the simplest one that we can get our hands around now, I hope it serves as a paradigm for the more complicated cases.

Chu  Peter it has been great as always to have you as our guest on Yale Cancer Center Answers. You provided a wonderful overview and review on the topic of chronic leukemias. Until next week, this is Dr. 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, visit 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 on the Connecticut Public Broadcasting Network.*