

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

OPERATOR: Hello, everyone, and welcome to *CML: Understanding Treatment, Monitoring Response*, a free telephone education program. It is my pleasure to introduce your moderator, Carson Jacobi.

CARSON JACOBI: Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society, thank you for choosing to spend this hour with us today and we welcome you to the program, *CML: Understanding Treatment, Monitoring Response*, featuring Dr. Eric Feldman. We thank him for sharing his time and expertise with us today and for his ongoing dedication to serving families touched by cancer.

We would also like to acknowledge and thank Novartis Oncology for their support of today's program and their continuous support of patient education initiatives.

You all should have received a packet in the mail including an agenda, a biography of Dr. Feldman, and an order form for The Leukemia & Lymphoma Society's materials. We encourage you to look through those materials at your leisure if you have not already done so. You can also find an evaluation form to fill out for today's program. For nurses and social workers, you can receive one hour of continuing education credit and all participants may visit our online evaluation center at www.LLS.org/eval to complete your evaluation online or mail it in the enclosed self-addressed envelope. I will provide an evaluation code for nurses and social workers at the end of our program today.

After Dr. Feldman's presentation we will open up questions from all of you, our telephone audience. And we have over 1,100 individuals registered for our program today from across the United States and some international participants, and they're from Australia, Canada, Venezuela, Lebanon, India and Kenya. A special welcome to all of you.

If we are not able to get to your questions today, you can call The Leukemia & Lymphoma Society's Information Resource Center. If you've been on the programs before you know we refer to that as the IRC. And the toll-free number included in your packet is 1-800-955-4572. Calling this number will connect you with an oncology professional who can answer your questions, help you obtain information or order free materials specific to your needs. And the IRC's hours are 9 AM to 6 PM, Eastern Standard Time, Monday through Friday.

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

CARSON JACOBI:

We are audio taping and transcribing today's program for posting on the LLS Web site in several weeks. This provides an opportunity to read or listen again to today's presentation, especially to follow up on any terminology or therapy that you may have missed.

Before I turn the program over to Dr. Feldman, I'd like to introduce The Leukemia & Lymphoma Society's President and CEO, John Walter, who is on the call today to welcome you and share a few words with you. John, thanks for joining us.

JOHN WALTER:

I would like to add my welcome to all the patients, caregivers and healthcare professionals on the call today. We are fortunate to have as our presenter Dr. Eric Feldman, a physician and researcher who is internationally recognized for his work in the development of new therapies for the treatment of leukemias. We appreciate Dr. Feldman's dedication to supporting the mission of The Leukemia & Lymphoma Society through his research and care of patients living with CML. I wish to thank him for taking the time out of his busy schedule to provide us today with an overview of treatment and monitoring for CML.

The Leukemia & Lymphoma Society is committed to bringing you the most up to date information about your blood cancer. We know it is important for you to stay current, so that you can work with your healthcare team to determine the best options for the best outcomes. Our vision is that one day the great majority of people who have been diagnosed with a blood cancer will be cured or they will manage their illness with good quality of life.

Since its founding in 1949, LLS has invested more than \$600 million for research, specifically targeting blood cancers. We will continue to invest in research for cures and programs and services that improve the quality of life for patients and families. This teleconference is one step on the road of your journey to managing your life with CML.

Thank you and I'll turn the program back over to Carson.

CARSON JACOBI:

Thanks so much, John.

I now have the pleasure to introduce our speaker, Dr. Eric Feldman. Dr. Feldman is the Professor of Medicine and Director of Hematological Malignancies at Weill-Cornell Medical College at the New York Presbyterian Hospital in New York, New York. Dr. Feldman is internationally recognized for his work in the development of new therapies for the treatment of leukemias

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

CARSON JACOBI: and related bone marrow disorders. He has led or participated in the conduct of numerous clinical studies, several leading to U.S. Food and Drug Administration approval of a number of anti-cancer agents, including most recently imatinib in chronic myeloid leukemia and lenalidomide in myelodysplastic syndrome. You can read further about Dr. Feldman in the biography in your packet.

Dr. Feldman, we're so happy to have you with us today and I'd like to turn the program over to you.

DR. ERIC FELDMAN: Thank you, Carson, for that wonderful introduction. And John, thank you for those words. And a thanks to The Leukemia & Lymphoma Society for putting this program together.

Welcome to everybody. It's a beautiful sunny spring afternoon on the east side of Manhattan.

What I want to do is talk about several issues related to chronic myeloid leukemia (CML) and I thought I would start by reviewing back to the causes of CML because I think our understanding of this disease and how we treat this really stems from that initial finding of what initiates or causes chronic myeloid leukemia.

And it's our understanding that CML is caused or initiated by what we call a reciprocal translocation of chromosomes. By that we mean in the chromosomes we have chromosome 9 and chromosome 22, part of our normal chromosomes. But in patients with CML, a piece of chromosome 22 breaks off and joins chromosome 9. And a piece of chromosome 9 breaks off and joins chromosome 22 and this is this reciprocal translocation and was named the Philadelphia chromosome because the researchers who found this were from Philadelphia.

But more importantly, what we know is on chromosome 9 there is what we call an oncogene called ABL. And on chromosome 22 we have a region of genes called the breakpoint cluster region or BCR. And when this rearrangement of chromosomal material takes place, we now have put together the ABL oncogene next to this area of the chromosome 22, the BCR or breakpoint cluster region, forming this new gene, the BCR-ABL gene. And this gene makes the protein which we also label as BCR-ABL.

Now what's important is this protein is what drives this disease because the protein has activity that we call tyrosine kinase activity. And what kinases do is help send signals to the cell, telling the cell to keep growing. Normally our cells

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

DR. ERIC FELDMAN:

are under tight regulation. Certain signals tell a cell to grow, some signals tell it to stop growing. When you have this mutation, this new gene, all of a sudden you have a turned on cell that is not responding to off signals. And so we have this unregulated growth of the cell.

And this leads to two problems. Initially we see the manifestations of the disease in terms of laboratory signs such as elevated white blood cell count or sometimes elevated platelet count, and we see signs and symptoms in the patient because of the uncontrolled growth of the white cells, the spleen tends to enlarge, people can develop weight loss, loss of appetite, fatigue. Those are the symptoms and signs.

But even more important than that initial event that occurs, is that when you have unregulated growth of a cell, that cell is what we label genetically unstable. And thus it is susceptible to additional mutations. And those mutations take a disease that starts in a slow and what we say a chronic phase, and at some point when these additional mutations happen, it starts to accelerate and resembles an acute leukemia. And at that point it is very difficult to treat and we lose patients because of that.

So our real goal in a sense is to get rid or to suppress the growth of those leukemic cells with their BCR-ABL protein activity.

Now in the past, and we still do, we can do one thing, we can kill cells completely. We can destroy the bone marrow and replace it with someone else's bone marrow and that's a very effective treatment, a bone marrow transplant or stem cell transplant. However, it has lots of side effects. Not everybody has a donor.

So for a long time everybody was looking for a new approach and then, of course, initially interferon was available and that did help suppress some of the growth of these BCR-ABL cells, but the great development and the great leap forward for treatment of chronic myeloid leukemia came with the development of the tyrosine kinase inhibitors and specifically the first one being imatinib or Gleevec®. And that, of course, is a direct inhibitor of the BCR-ABL protein and thus when you treat patients with CML with that drug, you suppress the growth of those cells. And when the cells are suppressed and don't have that drive, they disappear and the normal cells can come back.

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

DR. ERIC FELDMAN:

So the whole goal in a sense of all treatment is to ensure as complete as possible suppression of this BCR-ABL activity. And we know that's important because the initial event of CML, people can live with. The chronic phase is not difficult to live with and we've known this for a long time, as long as you control the white count. But what we have to do is prevent the secondary event, the acceleration of the disease to leukemia, acute leukemia. And we need to ensure complete suppression of BCR-ABL because this puts a cell that has uncontrolled growth and susceptible to new mutations now under regulation and not susceptible as much to the mutations.

So the whole goal and the goal of monitoring for the response is to make sure that we are keeping this disease in check and that it does not have a chance to go to these accelerated phases. And much the same way I would say for a patient who has developed hypertension or high cholesterol, as long as you control that and monitor it and keep things under control, the sequelae of those diseases won't happen, the heart disease, etc. So we look at this in the same way, that drugs like imatinib can suppress this and prevent it from moving into the advanced phases.

Now, of course, it's important that we make sure this is happening and therefore we need to monitor response very carefully because we have to show during treatment that we are achieving the necessary suppression of the disease. And so we look at a number of factors.

The first thing we look at, we want to see, is a complete hematological remission. And this means that all the signs and symptoms of the disease go away. The spleen shrinks, the white blood cells return to normal. And when you look at the blood counts, they look normal. This does not mean that the disease has gone away completely, but it gives us two things. It gives us initial knowledge that the disease is responding to treatment, so that within the first three months we like to see that the blood counts return to a normal phase. But also it gives us an opportunity to relieve symptoms. Of course, if patients are having symptoms from high white count, big spleen, those will go away. And also gives us a time in this initial period to assess any potential side effects. Because some of the side effects of these drugs, we can talk about that at the end, do occur early and can be modified early by certain treatments.

It is rare not to get a complete hematological remission. Most patients will do. And that is including with drugs like Gleevec, but even before with chemotherapy drugs like hydroxyurea or busulfan or even interferon. And so it's rare not to get this response.

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

DR. ERIC FELDMAN:

It is important in the first months to monitor the levels of the blood as they go down and we usually get blood counts once a week until we achieve this complete hematological remission.

The reasons for not getting a complete hematological remission are not entirely clear. There are some patients who have very resistant leukemia for unknown reasons, but that's very uncommon. We find our biggest problem is compliance in that some patients, for whatever reason, are not always taking their medication and this, of course, can lead to problems. Because we do want to control the disease.

Just as a side point, we sometimes see a patient who is not responding well or having unexpected side effects and in that setting, sometimes getting a level of the drug, the imatinib or Gleevec level, may help us identify patients who, for whatever biochemical reason, are not getting good enough levels and therefore not getting a response. Or may be getting too much toxicity from a very high level. So that can be helpful there.

So our first landmark is to achieve a complete hematological remission and we usually want to see that by three months. The most important landmark, however, is the achievement of a complete cytogenetic response. Now what we mean by that is when we do a bone marrow for cytogenetics, we look at the chromosome and the number of chromosomes that have this translocation, the 9;22 translocation. And so we count them. And at presentation most patients are 100 percent Philadelphia chromosome positive, 9;22 positive. Although there are some patients who have less than 100 percent at presentation. What we want to see is complete clearance of all those positive cells when we do the cytogenetic evaluation. And the reason is, is that we know this from experience, not only with bone marrow transplant, but with interferon and now with the tyrosine kinase inhibitors, that this is an important landmark to predict long-term outcome. In that patients who are treated, who achieve a complete cytogenetic remission that is durable, so far have had very little progression to the advanced phase. And the data for the tyrosine kinase inhibitors, particularly imatinib, shows that overall the majority of patients do achieve complete cytogenetic remission and most of them are durable. And if you achieve that, the likelihood of progressing at this point is quite low. And so that is our, in a sense, gold standard of response, to achieve that cytogenetic remission.

The next level of response that we look for is what's called a molecular response. Now this is still in a sense a work in progress. And the idea is that

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

DR. ERIC FELDMAN:

even in patients who have complete cytogenetic remission, they still may have low levels of leukemia cells that are undetectable by the cytogenetic examination. And therefore we might be missing patients who still have disease that could lead to relapse.

Now there is a technique, the polymerase chain reaction, which can detect levels of disease below the ability of cytogenetics to detect this. And this is what's called the molecular monitoring by quantitative PCR. And from data from the original studies with imatinib and now from other institutions as well, it has been shown that patients who have what is called a major molecular response, do extremely well. And what we mean by a major molecular response is that a 3-log reduction in the levels of the protein in the blood. So that if we say that the level would be 100 percent at baseline, that we would want to see .1 percent or less during treatment for the chronic myeloid leukemia with imatinib or other drugs.

And so we can see if we look at our experience to date, that patients who both achieve a complete cytogenetic remission and a major molecular remission, have a failure rate that's close to zero. Meaning that all those patients have remained well without any signs of progression.

However, patients with complete cytogenetic remission, even if they don't get a major molecular remission, are still doing quite well with close to a 97 percent success rate, out to six, seven years now. So the difference between a major molecular remission and a non-major molecular remission, as long as we have a complete cytogenetic remission, is not that different.

However, if we don't get a complete cytogenetic remission, then there is an increased failure rate. Still most of those patients are doing well, but in the 80 percent to 85 percent range is where those patients would end up in terms of staying in remission and not progressing.

So we do believe that the complete cytogenetic remission is really the most important finding and a major molecular response is helpful as well. And it remains to be seen whether that is important or not.

One of the problems with the major molecular response data is that we still don't have a fully standardized process that can be relevant across many laboratories. This is being worked on.

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

DR. ERIC FELDMAN:

There are also problems because the cells sometimes have to be shipped to outside labs and the transit time can lead to degradation of the protein and false negatives. So this is still a work in process. We still feel that a complete cytogenetic remission is the most important.

Monitoring by molecular means is helpful in that it can avoid having to do lots of bone marrow exams. So once you achieve a complete cytogenetic remission, then perhaps marrows may be less helpful and that you can look for the molecular response. And as long as it's low and stable, everything should be well. And if we see it go up that would be an early warning that perhaps there's a loss of response.

But really, and I think at this point I think most would agree, that clinical decisions on changing treatment should be really based on loss of a cytogenetic response, not on changes in the molecular response at this point because the validity of the molecular test is still not as clear as the cytogenetic response.

But a major molecular response, of course, is important, too. Because not only do we not see progression, but also there's a very low rate of mutations in those patients. And what we mean is some patients along the way, being treated with imatinib, who develop resistance, we find mutations in that their protein, their BCR-ABL area is no longer binding the drug imatinib. And therefore imatinib stops working. And so in a sense having a major molecular response would predict that this is an unlikely event to happen. But time will tell the importance of the major molecular response at this point. As time goes by, if we see that this test is more predictive than cytogenetics, then it will become more and more relevant.

So in summary, to say when should we think about switching, what are the signs that the initial treatment with imatinib is not doing its job? One would be certainly if we have intolerable side effects to imatinib, and of course, we can discuss that in the question period. But certainly a lack of complete hematological remission at three months, a lack of any cytogenetic response at six months, a lack of a major cytogenetic response at 12 months, meaning that under 35 percent of the cells are positive, and then we definitely want to see a complete cytogenetic response by 18 months. And whether looking at a lack of a molecular response is important, that again needs to be resolved in future studies.

So basically there are a number of questions that have come up and I'll sort of in the last five minutes of this formal presentation, I'll just go through some questions that come up in terms of where we are in terms of our management.

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

DR. ERIC FELDMAN:

So initially we know the standard of care is imatinib at 400 milligrams per day. And that has been the standard and continues to be the standard. Now the question, of course, is it better to start at higher doses of imatinib or maybe to start with new agents instead, some of the new agents such as dasatinib or nilotinib, may be more powerful inhibitors and work in resistant cases and maybe we should try them up front. And there is a certain rationale for that, in that if we get a faster response or a deeper response earlier with the new drugs, will that mean that there will be less time for mutations to occur and so in the long run we will be better off.

This is an important question and it makes sense from a scientific point of view. However, we just don't have enough data to really say that starting with a new drug or starting at a high dose of imatinib, like 800 milligrams, is clearly better. At least to the limits of our data right now, to decide that.

So for now, 400 milligrams should still be considered the standard of care. But I think for the rationale I just mentioned, there will certainly be interest in looking at the new agents up front or the higher doses of imatinib to see if these drugs in the long run will be better and time will tell.

Again the same question is whether switching earlier for what we would consider suboptimal responses. So what I had listed before were the responses that we would consider were not good at all and would suggest definite resistance developing. There are some less optimal responses, that maybe not being in complete cytogenetic at six months as opposed to any cytogenetic, should that mean we should switch? The question is should we switch faster? Again, the same idea is that the quicker we get control of this disease, the better. And again it makes sense, but we just don't have the data to support it.

Another question comes up, is what to do when we develop imatinib resistance? Should we look for a mutation to help guide our treatment? We do have very good second-line treatment drugs such as nilotinib and dasatinib. There are some mutations that occur in CML patients that are resistant to both. And I think that for certain groups of patients it's helpful to know, particularly if they are young and have a potential for a bone marrow transplant. Because we still have to remember that there are some patients who may not be able to be cured right now with a tyrosine kinase inhibitor and therefore we should not forget that bone marrow transplant still has a role in young patients.

How do we manage patients in second-line? At this point we definitely suggest trying a second-line approach when there is imatinib resistance. And many of

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

DR. ERIC FELDMAN: those patients will achieve complete cytogenetic remission and may be able to avoid transplant, but we should be very vigilant in those patients as well.

Finally, there are some new agents. One drug in particular, is called AP24534. It's being tested in clinical trials, particularly for those patients who have the T315I mutation. And we will wait to see how active this drug is.

There's another very old drug that came out of China many years ago, called homoharringtonine. And in a recent paper showed that this drug may selectively block the CML stem cell. And by that we mean that there may be a very, very early cell that initiates this disease, possibly even before the Philadelphia chromosome. And that this cell may be the one that we can suppress. And if we can, that would be even more helpful because that could lead to in a sense, a cure, as opposed to control of the disease. But of course, these are laboratory studies and we need to see the clinical data.

So I will stop here and we'll have plenty of time for questions. Thank you.

CARSON JACOBI: Excellent. Thank you so much, Dr. Feldman.

It's now time for the interactive part of our program, the question and answer session. So before Lindsey gives you all instructions to enter the question and answer queue, I would like to remind you all that because we have so many on the line, for everyone to benefit, if you can please keep your questions general in nature and brief, and Dr. Feldman will provide an answer general in nature. And your phone line will be muted after you ask your question, so Dr. Feldman can respond.

So if you can please give instructions to our audience, so they can ask a question.

OPERATOR: To participate in the call by asking a question, please dial star-1 on your keypad. We will take questions in the order they are received. Be aware that due to time constraints, we can only take one question per person. Once your initial question has been voiced, the operator will transfer you back into the audience line. Again, to participate in the call by asking a question, please dial star-1 on your keypad.

CARSON JACOBI: Great. We'll take our first question, please.

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

- OPERATOR: Our first question comes from Linda from Delaware.
- LINDA: Hi, I have a question for someone who has been on Tasigna® for about a year and it appears to be having too serious side effects with bad pain, which at one other point led to pancreatitis. So we're interested in what will be the next step. Another person with CML said that she's getting some new drug being tested at Hershey Medical Center. Is that the AP25314? Or do you happen to know what the new drug is that's being tested at Hershey Medical Center?
- DR. ERIC FELDMAN: Thank you for the question, Linda. No, I don't particularly know what drugs they're working on at Hershey. It could be the AP2354.
- Now the question about the pain. We do see some side effects to Tasigna. All the tyrosine kinase inhibitors do have some side effects, of course. I'm not particularly aware of pancreatitis being a big risk. It certainly is a rare complication. I'm not even aware that that is definitely related to the Tasigna. But one option, of course, is that there is a second-line drug also called dasatinib and some patients tolerate that better. And also another drug called bosutinib is under clinical development and is available in some studies for patients who are intolerant to or resistant to the other drugs. So I'm not exactly sure what's going on at Hershey, Pennsylvania, but I'm sure if you called them you could get that information.
- CARSON JACOBI: Linda, thank you for the question. We'll take another question, please.
- OPERATOR: The next question comes from Dave from Canada.
- DAVE: I have the following question. Do you see any advantage in achieving PCRU over a 3-log reduction? The reason I ask the question, I know there are many hematologists/oncologists who will have the patient increase their dose, say from 400 to 600 or higher, in order for the patient to get to PCRU. So could you comment, if that's really necessary?
- DR. ERIC FELDMAN: Thank you, Dave. That's an important point. PCRU meaning undetectable. So you have to understand the limits of the test. Undetectable is sort of a made-up term, it's arbitrarily used to say at this point on our PCR analysis, if we have to go to this many cycles of amplification, we're going to call it undetectable. So it's not really that different. And of course, because the difference is the technique and there may be degradation in the protein and false negative, false positive – there's no data suggesting that beyond a 3-log reduction there's an advantage of being undetectable.

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

- DR. ERIC FELDMAN: Certainly patients, and as doctors, we all feel much better when we have an undetectable patient. That sounds really great. But I think having a 3-log reduction is fine, and there's no evidence that going further with upping the dose makes a difference. And I'm not sure I would support that.
- CARSON JACOBI: Dave, thank you for the question. Let's take another question, please.
- OPERATOR: The next question comes from Sharon from New York.
- SHARON: Hi. I just want to express my gratitude to everybody in the field because I had CML 32 years ago and I had a bone marrow transplant in 1991. And I'm blessed to be able to see many of my friends now survive CML. And blessed to be able to be alive. And very grateful for all your research, for the help The Leukemia Society has given me. And for just everybody out there who's been supportive to me. And I just want to say thank you to the doctors, nurses, social workers, staff everywhere and all my friends. Thank you.
- DR. ERIC FELDMAN: Thank you, Sharon, for that. I think it's very helpful for everyone to hear from patients who are out these many years. We always love to hear from our patients who are doing well. And I think this points out that bone marrow transplant has been and is still a very effective treatment for some patients. And we still offer transplants in some select instance. However, with imatinib now I would say that for the majority of patients, a trial of imatinib up front should be considered before a bone marrow transplant. But that's great to hear from you.
- CARSON JACOBI: I echo that, Dr. Feldman. Sharon, thank you for your sentiments also. It's always wonderful to hear from patients. And you know, just being on the call today, that The Leukemia & Lymphoma Society is steadfast in our mission to fight this disease and to help patients live long and happy and prosperous lives. So thanks for being on and sharing those thoughts.
- Let's take another question, please.
- OPERATOR: The next question comes from Gerri from Washington.
- GERRI: Hi, Dr. Feldman, thank you so much for taking my call. My question is, I'm doing well on my Gleevec; I have a horrific side effect, though, with the watery eyes and the fluid retention. And I was just wondering if there's anything new and up and coming to help stem that. My eyes now are to the point that they almost swell shut daily from fluid retention and just wanted to know if anything new is up and coming.

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

- Dr. Eric Feldman: Thanks, Gerri, for the call. Watery eyes or edema around the eyes, those are two separate things. The watery eyes I sometimes think of as conjunctivitis and that's a rare side effect. And unfortunately, one of those that's very difficult to get rid of because even the second-line drugs we sometimes see have similar effects. So we've had patients who've had this conjunctivitis and tried to switch from imatinib to nilotinib to dasatinib and it didn't seem to help.
- The fluid retention is also difficult. It depends on how severe it is. For some patients mild diuretics can be helpful. If it's around the eyes, I've heard that, believe it or not, putting Preparation H under your eyes at night, as long as you don't get it in your eyes, has been helpful. And there are some caffeine-based eye creams, I'm told, by Sandy, our nurse practitioner, that can help with this. But those are sometimes difficult.
- If it becomes problematic, I think switching to a second-line is not a bad idea. You know, these second-line drugs are very active, we have very good data on them. Before we had them, we kept everybody on Gleevec and tried our best to mitigate the side effects. Now that we have very good second-line drugs, we feel more easy about switching when we have recalcitrant side effects.
- CARSON JACOBI: Gerri, thank you for the question. Let's take another question, please, Lindsey.
- OPERATOR: The next question comes from Mary from Colorado.
- MARY: Hi, Dr. Feldman, thank you so much for your time. I just wondered if you could briefly talk about some food and drug interactions with Gleevec.
- DR. ERIC FELDMAN: Did you have any specific question about ...
- MARY: I recently had a little blip in my PCR and my bone marrow biopsy. And so I kind of monitored what I was eating and some of the – even vitamins. And I had pulled up a list of like 11 pages of Gleevec drug interactions that I don't know if they cause the Gleevec maybe not to work as well. Have you heard of any?
- DR. ERIC FELDMAN: Yes. So there are some drugs that we know can affect the level of Gleevec. Things like Dilantin® or even some over-the-counter medication like St. John's Wort, for example, have shown to decrease levels. We've been very interested in this because we've had the same experience, where a patient is doing extremely well, everything going great, and all of a sudden there's a blip, as you say, and they've just started a new drug. So I think that's very important for you to get an imatinib, if you're on Gleevec, to get a Gleevec level to see

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

DR. ERIC FELDMAN: what's going on because it's possible that something you're taking could change that.

I don't know about any specific foods that I've heard of that can do that. But obviously there are many food supplements, over-the-counter things in health food stores that people take, that may have things in them that can change levels.

This is one area where I think if you have an unexpected change, is to get a level if you're on Gleevec and see what's going on.

CARSON JACOBI: Mary, thank you for the question. We'll take another question, please.

OPERATOR: The next question comes from Tina from Connecticut.

TINA: Good afternoon, everyone. Thank you so, so much as well for everything. Quick question, is, how reliable are the levels testing? And any clinical trials for monitoring going off Gleevec? Seven years and complete remission for me, undetectable.

DR. ERIC FELDMAN: Thank you, Tina. That's great, that's great response. So the levels, as we talked about the molecular levels, it's still a work in progress. Within laboratories, within individual laboratories, it's quite reliable and there are several commercial laboratories or other academic institutions that do this test regularly and have very reliable data. The problem, of course, is the intra-laboratory changes. And so we say that you should be monitored within one laboratory right now because we haven't really worked out an international standard for conversion between labs yet. But within your own laboratory, if you're testing it and you're coming back undetectable or low, low levels, then that is a very good sign that there's no activity of leukemia or minimal.

Now coming off is always the question. Nobody wants to take a drug forever and there's always the cost involved. There are some studies and there was some data presented by the group in Europe, I think in Germany, where they did take patients who were in your situation with completely undetectable, durable undetectable, and some were taken off the drug. And the experience has been mixed. Some did relapse and had to be retreated, but fortunately did respond to retreatment. Some, however, have remained well so far without any signs of disease. So it's possible, there is a subset of patients who could be taken off the drug.

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

DR. ERIC FELDMAN: I think at this point we still don't know and we generally counsel to continue as long as there's no side effects that are problematic. We have taken a cautious approach with this, just because we understand that these drugs may not – you know, they suppress the clone of leukemia, but they may not eradicate it entirely. And we are somewhat afraid of letting leukemic cells start to grow again because, as we said in the beginning, that's where genetic instability comes from and new mutations.

So I think it's a great idea to look at this question, but off of a clinical trial I would not stop your Gleevec.

CARSON JACOBI: Tina, thank you for the question. You did mention clinical trials. Just for everyone to know and for your benefit, if you want to learn about a clinical trial there is an online service called TrialCheck[®] on The Leukemia & Lymphoma Society's Web site. You can also talk to one of the Information Resource Center specialists, who can do a trial search for you or can answer more questions about a clinical trial.

Let's take another question, please.

OPERATOR: The next question comes from Richard from California.

RICHARD: Hello, Doctor, thank you for the time. I've had CML for five years. I have a JAK2 mutation and I've been on interferon and cytarabine and Gleevec for that entire time. And I'm wondering if you could expand a little bit more on what's happening with drugs for specific mutations.

DR. ERIC FELDMAN: Before you get off, you're on all three? You're on Gleevec plus interferon and cytarabine, or just on ...

RICHARD: Yes, I'm on all three. I do injections of cytarabine and interferon three times a week and then I take 600 units of Gleevec a day.

DR. ERIC FELDMAN: And is that because the Gleevec alone didn't work?

RICHARD: That's correct.

DR. ERIC FELDMAN: And do you still have the pH-positive cells or is that because the other, the JAK2 positive cells are still there? I'm not quite understanding the rationale for all three drugs.

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

- RICHARD: There is still, from what I understand, pH activity. I did a FISH test about two weeks ago and the cells were elevated about 5 percent.
- DR. ERIC FELDMAN: And you've not tried the second-line drugs?
- RICHARD: No, she hasn't.
- DR. ERIC FELDMAN: This is an interesting question of how to manage. Again, we have to go back to our endpoints, that we want to achieve complete cytogenetic remission and at five years, we would definitely not want to see 5 percent positive cells floating around. Interferon can be effective, it's been a long-time drug that you could add, and cytarabine you could add. But if you're still not in remission I would suggest switching to one of the second-line drugs because they definitely have shown the highest response for patients who are imatinib-resistant. And you want to do it before the disease starts to relapse because the best results for the second-line are before hematological relapse, so when you're still in cytogenetic relapse.
- The JAK2 mutation is unclear. There are some patients who have that. Whether that has relevance to the activity for Gleevec or other drugs in CML is unclear. It's a rare phenomenon and we just still don't understand what it means entirely.
- CARSON JACOBI: Richard, thank you for the question. We'll take another question, please.
- OPERATOR: The next question comes from Ari from Pennsylvania.
- ARI: I've been diagnosed with CML in 2007. And I've achieved undetected, I guess remission, last July, it took a year. And I have been good ever since. And I'm still having trouble tolerating Gleevec. I'm down to 200 milligrams a day and my blood tests are still coming back good. But I was wondering if there's another way to take Gleevec such as a patch or an injection or an IV once a week? I still have problems with my stomach a lot.
- DR. ERIC FELDMAN: That's the reason why you're on a lower dose, because of nausea or ...
- ARI: Yeah, I'm on 5 milligrams of Marinol® twice a day, just to keep the nausea at bay because I was throwing up and everything. And I still have diarrhea.
- DR. ERIC FELDMAN: This is a scenario that we see often as we do get side effects and the physicians attempt to lower the dose to try to get rid of them. But as you can see from the experience, that even at 200 she's having side effects. I'm not so

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

- DR. ERIC FELDMAN: kept on lowering the dose. The problem at 200 milligrams is that the disease may relapse. We know from experience that that level may be too low to control the disease. I would definitely, if you cannot tolerate Gleevec and it sounds like your doctor has tried all the drugs for nausea to try to get rid of it, I would switch to a second-line drug, nilotinib or dasatinib, because you may not have the same side effects. But staying on 200 milligrams is of great concern to me.
- CARSON JACOBI: Thank you for the question. We'll take another question, please.
- OPERATOR: The next question comes from Mary from New Jersey.
- MARY: My question has been answered. Thank you very much, Dr. Feldman.
- DR. ERIC FELDMAN: You're welcome.
- CARSON JACOBI: Thanks, Mary. Another question, please.
- OPERATOR: The next question comes from Michele from Massachusetts.
- MICHELE: Hi, thank you everybody, again. My question was similar to the last person's question. I was diagnosed a year ago, 7 percent positive, and I was put on Gleevec and had an extreme response that caused hepatitis in my liver. It took six months for my liver to heal. I started on Tasigna about four months ago. And he started me off on a low dose and is monitoring me very closely. He started me on half dose. I was having extreme discomfort with that and he lowered it down to the lowest possible dose, 200 milligrams of Tasigna, which I feel much better on. And I've had a full hematological response since the first week. But I am concerned or I'm wondering how concerned I should be about the low dose and where to go.
- DR. ERIC FELDMAN: What's the side effect you're having on the Tasigna? It's your liver again?
- MICHELE: No, my blood work was okay, but I was having extreme burning throughout my back, I was having nausea and diarrhea and headaches. But the extreme burning. And it started out pretty strong, but it got extreme. I couldn't sleep or walk.
- DR. ERIC FELDMAN: How old are you, Michele, if I can ask?
- MICHELE: I'm 45.
- DR. ERIC FELDMAN: Thank you. We see this sometimes. There are some people and in the Gleevec trials, less than 5 percent, who just cannot tolerate Gleevec for a variety of things. Liver abnormalities sometimes have been severe. Bone pain or back

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

- DR. ERIC FELDMAN: pain or muscle aches, cramps, nausea. We see this. It's rare that we can't get around it. But the problem, as I mentioned to our last caller, is that going on a low dose is a concern because we're really not giving, in most cases, or maybe not giving, the effective enough dose of the drug to get rid of the leukemia. And so we have to try something else. And I would suggest maybe dasatinib is also available or if not, bosutinib may be available on clinical trial. But I would worry again, as I worry with the Gleevec 200 milligrams, Tasigna 200 again is also a dose that may not be sufficient to control leukemia. And so I would try something else if you can't tolerate higher doses of the Tasigna.
- CARSON JACOBI: Michele, thank you for the question. Let's take another question, please.
- OPERATOR: The next question comes from Jack from Idaho.
- JACK: Hi, Dr. Feldman. I was diagnosed in March of '07 and started with Gleevec treatment and had good results. Never did get a complete response. And about 12 months to 18 months down the road, it started going the other way. So my doctor referred me to OHSU leukemia center. And he right away put me on the drug Sprycel® and I've had a complete response in three months, thank God, and thank you guys. And just kind of curious, if I might have a mutation to this one. I had the I513 mutation.
- DR. ERIC FELDMAN: This is always the question of – well, two questions, of course, is should we be doing routine mutational analysis in patients who are imatinib-resistant, and of course, there's two minds. One is that yes, because we can pick up some mutations that won't respond to any drugs like the T315I and, of course, those patients would have to go on to a clinical trial or maybe a transplant, if they're young enough. But for all the others, most of them thankfully do respond to dasatinib or nilotinib. And therefore it may not matter. We routinely look for the mutation, just to have that information. But the fact that you've responded to Sprycel or dasatinib is a good sign, meaning that even if you had a mutation, it's a probably a sensitive one. And the data would suggest that these responses are durable, although we don't have as long a follow-up as we do with the Gleevec.
- I would make sure you do the molecular monitoring very carefully because you did become resistant to Gleevec and we always worry about resistance to the second-line as well. Hopefully that won't happen. But I think very frequent monitoring, at least every three months, to see what's going on would be important.

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

CARSON JACOBI: Jack, thank you for the question. We'll take another question, please.

OPERATOR: The next question comes from Larry from Virginia.

LARRY: Yes, Dr. Feldman, I'm a physician who's been diagnosed with CML for the last 12 years. Within a year I went into complete cytogenetic remission on interferon and have remained so. So I'm still taking interferon. When I come out of that remission, what are the data in terms of Gleevec usage and what are the statistics regarding how long I may stay in remission on the interferon?

DR. ERIC FELDMAN: Yes, thank you for that question. Interferon, as you know, has been around a long time to treat CML. And I still have patients like you, who have remained on interferon and have done well and when imatinib became available, because they were doing well, decided to stay on interferon rather than switch over. Although interferon has a lot of side effects, there are some people who tolerate it very well.

I would say – we often do, what we do is taper down the dose of interferon, so that we can get rid of some of the side effects. The results of imatinib in patients who are interferon-resistant or intolerant are good and that was the basis for the initial approval for Gleevec, was in the interferon-intolerant or resistant group. And the results are very good. And we still follow a number of our patients who are on that original trial in 1999 and they're all doing quite well. So I think the likelihood is, first of all, that you may not relapse. There are many patients who have stayed in complete remission on interferon or even on minimal doses and have not relapsed. But if you do, the results with imatinib, Gleevec, or others are quite good.

CARSON JACOBI: Larry, thank you for the question. We'll take another question, please.

OPERATOR: The next question comes from Francis from North Carolina.

FRANCIS: Dr. Feldman, some hematologists, I understand, instead of doing a bone marrow six months after initiation of therapy, do a FISH test on the blood. Is that advisable?

DR. ERIC FELDMAN: I would say no. I think that although the FISH, fluorescence in situ hybridization, is a way of looking at the BCR-ABL population of cells in a different way, different technique, it's an effective technique. Unfortunately what we've seen is sometimes it cannot correlate well with the bone marrow cytogenetics for some reason in patients on Gleevec and therefore we have sometimes seen

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

- DR. ERIC FELDMAN: negative results by FISH, where we have positive results in the bone marrow. So I still think the bone marrow cytogenetics at six months and at one year is still important to do, to make sure that we are achieving the complete cytogenetic response. Once we get a complete cytogenetic response, then I think the RTPCR, the molecular testing, is much more helpful than the FISH. So we don't do FISH analysis that much. We do the bone marrow cytogenetics and then we go to the RTPCR.
- CARSON JACOBI: Francis, thank you for the question. We'll take another question, please.
- OPERATOR: The next question comes from Steven from Pennsylvania.
- STEVEN: Hi. Dr. Feldman. I've been PCR negative, 3-log, for almost seven years, I was fortunate. I just wanted to know, you always use the word undetectable. I mean, after seven and a half years, is it undetectable or is it gone? And if it is, are they ever going to reduce the dosage?
- DR. ERIC FELDMAN: So that's a good question. First of all, the technique, the polymerase chain reaction works – we amplify any cells that are in there and you go through cycle after cycle. So it's arbitrary to say okay, if we've hit this cycle and we haven't seen any positive cells, any protein, we'll call it undetectable. And so that's sort of an arbitrary figure. So undetectable means that you have an extremely deep response. And whether the disease will come back at this point, so far the data would suggest no, that patients who have remained on Gleevec or other drugs and achieved that, have not relapsed.
- Now can you lower the dose? This is again an unknown. Certainly if you're on 800 or 600 of Gleevec, you could probably go to 400. But anywhere below, even in some patients, okay at 300, but anything below 300 we worry about, that that is not a sufficient level to control. And if there are any cells left in the bone marrow that could lead to a relapse. So it's still an unknown question as to whether you could come off. And again, the other questioner asked about coming off and there are some trials in Europe looking at this question, but I think if you're tolerating it well, just keep going.
- CARSON JACOBI: Thank you, Steven, for the question. Actually thank you all for your questions. Our program has come to an end. An hour went by very quickly.
- If you can please help me thank Dr. Feldman. We are so grateful that he has donated his time to us today and we thank him for all the work he does every

CML: Understanding Treatment, Monitoring Response

Eric J. Feldman, MD

May 19, 2009 • 12:00pm ET

CARSON JACOBI: day in supporting families touched by cancer. We also would like to thank again Novartis Oncology for their support.

We hope that many of your questions were answered and that the information will assist you and your families in your next steps.

A reminder to fill out your evaluation form and we encourage you to complete your evaluation online again by using www.LLS.org/eval or you can mail your evaluation in the envelope provided. If you are a nurse or social worker, fill out your continuing education credit form, you must enter the code CML382.

Our Information Resource Center is open. The number is 1-800-955-4572. And our specialists are ready and available to speak with you or answer any other questions you may have.

So on behalf of The Leukemia & Lymphoma Society, Dr. Feldman and I would like to thank you all for sharing this time with us. Good-bye and we wish you well.

DR. ERIC FELDMAN: Yes, thank you.

OPERATOR: This concludes today's conference call. You may now disconnect.

END