

CML: What Every Newly Diagnosed Patient Needs to Know

Jorge Cortes, MD
September 15, 2009 • 12:00pm ET

OPERATOR: Hello, everyone, and welcome to *CML: What Every Newly Diagnosed Patient Needs to Know*, a free telephone/webcast education program. It is my pleasure to introduce your moderator, Carson Jacobi.

CARSON JACOBI: Thank you, Kayla, and hello, everyone. On behalf of The Leukemia & Lymphoma Society we thank you for choosing to spend this hour with us today.

We welcome you to the program *CML: What Every Newly Diagnosed Patient Needs to Know*, featuring Dr. Jorge Cortes. And we thank him for sharing his time and expertise with us today and for his 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 for their continuous support for patient education initiatives.

You all should have received a packet including an agenda, a biography for Dr. Cortes and an order form for The Leukemia & Lymphoma Society's materials. And we encourage you to look through the materials at your leisure. And if you registered online and are participating by computer, you've received these materials online.

You'll also find an evaluation form for you to fill out for today's program. For nurses and social workers, you can receive one hour of continuing education credit. I will have more information about our online evaluation center at the conclusion of today's program.

After Dr. Cortes' presentation, we will open up to questions from our telephone and computer audience. And we have over 1,100 individuals registered for our program today from across the United States and we have some international participants from Australia, Canada, Venezuela, Barbados, South Africa, India and Kenya. We welcome all of you.

Those of you participating by computer, you will only hear the audio for today's program with one or two title slides. If we're not able to get to your questions today, you can call The Leukemia & Lymphoma Society's Information Resource Center. The toll-free number, which is included in the materials in your packet, is 1-800-955-4572.

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CARSON JACOBI: This will connect you with an oncology professional who can answer your questions, help you obtain information or order free materials specific to your needs. The Information Resource Center's hours are 9 AM to 6 PM Eastern Time, Monday through Friday.

We are audiotaping and transcribing today's program for posting on The Leukemia & Lymphoma Society's 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 therapies that you may have missed.

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

JOHN WALTER: Thank you, Carson. I'd like to add my welcome to all the parents, patients, caregivers and healthcare professionals on the call today.

We are fortunate to have as our presenter Dr. Jorge Cortes, a world-renowned CML specialist. We appreciate Dr. Cortes' dedication to supporting the mission of The Leukemia & Lymphoma Society through his research, his clinical practice and his service as a member of both the LLS National Board of Directors and the LLS Scientific Advisory Committee. I wish to thank him for taking the time out of his busy schedule to provide us today with an overview of CML for the newly diagnosed.

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 a 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 their 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.

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CARSON JACOBI: Thank you, John.

I now have the pleasure of introducing our speaker Dr. Jorge Cortes. Dr. Cortes is the Professor of Medicine, the Chief of the CML Section in the Department of Leukemia at the University of Texas M.D. Anderson Cancer Center in Houston, Texas.

Dr. Cortes, we are thrilled to have you with us and I will turn the program over to you.

DR. JORGE CORTES: Thank you very much and good day, everybody. I am glad you are able to join. I think that these programs are extremely important because other than the remarkable therapies that we currently have in this disease, I think that one of the best tools that we have to achieve a good outcome and potentially a cure is good information. So hopefully this will help you with your journey with this disease.

I'm going to briefly go through some of the important pieces of information I think are important for any patient or any family member of a patient with this disease. And then we will open for questions.

One important thing that we need to remember today is that the outcome of patients, the natural history of the disease has changed significantly, where in the 1960s when there was the initial recognition of what we now know as the Philadelphia chromosome started, approximately 50 percent or half of the patients that were diagnosed with this disease would have died by about four to five years. And nowadays we're very fortunate that we have more than 90 percent of the patients still alive by that time. So clearly, that has been a major change in the outcome of patients and it's something that we really don't see much in other diseases.

One important thing that we need to do when a patient is diagnosed is to recognize what stage this patient is at and everybody knows that there are three stages. There's the chronic phase, which is where most patients are diagnosed at the beginning. There is an accelerated phase, which is an intermediate phase before going to what is called the blast phase, that some people call an acute phase or an acute leukemia, but it's more properly called a blast phase.

It is important to realize that for the proper staging of a patient at the time of diagnosis, you do need a bone marrow aspiration, you do need some blood tests to look at the percentage of blasts and basophils and all these things.

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DR. JORGE CORTES: Then within the chronic phase there is a staging system that we use that's called the Sokal classification and there are others, but this Sokal classification, which is just simple things such as the age and how large the spleen is and the basophils and the blasts. These can help you determine how likely it is that the patient may respond to therapy at the beginning, so it's a good additional tool to try to understand the potential outcome.

Also it is very important to remember that the diagnosis of this disease is made by the presence of what we know as the Philadelphia chromosome, which, as you know, represents a switch between chromosomes 9 and 22, where they exchange a little piece of their material. And every patient will have the Philadelphia chromosome, although in a few patients you cannot find it by the regular chromosome analysis, but you would find it in a more detailed molecular test, something that we call the PCR test.

There's a few patients, about 5 to 10 percent, that have what's called a variant translocation. That is instead of just two chromosomes, the 9 and the 22, they have a third and occasionally even a fourth chromosome involved, so that you'd see something that is a translocation, for example, between chromosomes 3, 9 and 22, and really any other chromosome can be involved.

Nowadays these variant translocations don't seem to have an additional worse outcome, although in the past they did have a worse prognosis.

The Philadelphia chromosome is very important because there's three main things that we know from the Philadelphia chromosome. One is that it causes the disease. There's experiments where we've been able to put this abnormal chromosome into cells and then give those cells to little mice in the laboratory and they get the disease. So it starts the disease. The other thing is that it's a marker of the disease. At the time of diagnosis not every cell in the bone marrow has the Philadelphia chromosome. It appears as it is, but it's just because these cells have an advantage, they grow faster and more. But we do have some normal cells. And during the course of therapy what is really important is to make sure that we're getting rid of all the cells that have the Philadelphia chromosome. So it's not only whether the counts become normal, but really most important, whether we are changing from the beginning, seeing almost all of the cells with the Philadelphia chromosome and very few, if any, without the Philadelphia chromosome or normal cells, to get to the point where we see all normal cells and no cells with the Philadelphia chromosome.

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DR. JORGE CORTES: And then the third reason why the Philadelphia chromosome is important is because these cells have become dependent on this abnormal chromosome and that can be used to our advantage and has led to the discovery of these treatments that specifically block the function of this chromosome. And without that function these cells die and that leads us to the remarkable responses that we see.

We also need to remember that are other diseases that sometimes can look alike, like CML. For example, there's a few patients that would not have the Philadelphia chromosome in chromosome analysis. As I mentioned, in many of them you will find, by an additional test, the PCR, you will find the joining of these two genes that come from chromosome 9 and 22. And in this case that's still CML.

If there is no Philadelphia chromosome by any test, then that is not the same disease. That's what we call a true Philadelphia-negative CML. And those patients would not benefit, for example, from the treatments we're going to be describing later today. And they're usually given more standard chemotherapy.

But there's another disease that's called CMML, that's chronic myelomonocytic leukemia, which is a different entity that also has a completely different therapy and we're not going to be able to focus on these other diseases in this discussion.

So regarding treatment, I think that going back to my initial statement of how much we have changed the natural history of this disease, we have now approximately eight years of follow-up since the first patient that received imatinib or Gleevec® as initial therapy for their disease. So now we know how we're doing after this long time. And the results continue being very, very good fortunately. We know that approximately 82 percent of the patients will get to what we call a complete cytogenetic response. That means that when you count 20 chromosomes in their bone marrow, none of them have the Philadelphia chromosome. And that we know from before Gleevec, when we used interferon, that that is the main marker that correlates with a better probability of being alive. And indeed, we have seen that that has happened with imatinib, with so many patients achieving this complete cytogenetic response, we have by seven to eight years nearly 90 percent of patients alive. And if you only considered the patients who died from CML-related issues, it's almost 95 percent of patients who are alive.

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DR. JORGE CORTES: Also very fortunately, the rate at which patients lose their response is declining over time, which is very good news. There's a few more patients, probably about anywhere between 3 to 5 percent per year, that may lose their response in the first two to three years, but then it goes down significantly to approximately 1 percent or less per year. So the responses tend to be very stable, at least with the time that we have been able to follow these patients. So this is very important because I frequently hear the statement that patients have heard from other patients or from some sources that say, "Well, I know that after five years the treatment is going to stop working," and that is not a true statement, that is not something that we see in the clinic. Fortunately we see that the responses continue being very durable and very sustained, well beyond the five years. And again, we have eight years of follow-up so far.

Now we do know that there are a few patients that do not get the response that we want and a few patients who do lose their response, so there are some patients that will need different treatments and the recent interest in improving the initial therapy, so that instead of having, let's say, two-thirds or 70 percent of patients doing very well after seven or eight years, we would like to improve that to 100 percent. So we will be talking about some of the approaches that we're using to try to improve these results.

One thing before I get to that, that's important to emphasize, is that there is a bit of a controversy on whether the time to achieve a good response is important or not. I think that there is growing evidence that indeed the patients who have the earliest responses tend to have responses being more durable. And not only that, once you get a response, the chances of progressing are much lower. Now patients who do not get a response, they may still improve their response, but there is still disease there that obviously you are concerned whether it may progress. So I think that nowadays we are interested in seeing if we can get more patients to respond as early as possible.

And there have been some recommendations on how we should grade the responses, whether it's an optimal response or a suboptimal response, whether the response is as good as we would like it to be or not. And that has to do with not only how well the response is, but also at what time after the initiation of therapy. And particularly important are the first 18 months of therapy, where we know which kind of results we want to achieve, what percentage of Philadelphia-positive metaphases are still acceptable at the different time points.

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DR. JORGE CORTES: I mentioned earlier that we do want to improve the results with therapy and one initial approach that was used was to use higher doses of Gleevec. So instead of starting with 400 milligrams, starting with 800 or at least 600 milligrams of Gleevec. And there are many studies that have suggested that you do get earlier responses with this approach. And there are a few studies which directly have compared higher doses versus standard doses. We're eagerly awaiting the long-term results of these studies because we do know that you do get earlier responses. What we need to see is that hopefully that would translate into more patients being alive and well after enough time. That will take a little longer to get to confirm that this is the case.

Now there are other things that we are exploring more recently. And as you know, there are new drugs, the second generation of what Gleevec is, and these are two drugs that have been approved recently for use in patients who have failed Gleevec. One of them is called nilotinib or Tasigna®. The other one is called dasatinib or Sprycel®. These are drugs, and we're going to discuss them a little later, that work when Gleevec fails. But we've also started using them as initial therapy to see if we could even improve further the outcome of patients at the time of diagnosis. And the results have been actually very impressive.

So for example, after six months of therapy when with the standard dose of Gleevec you get about 50 percent of patients without the Philadelphia chromosome anymore, with these new drugs you get over 90 percent of patients already without the Philadelphia chromosome by six months. So we're very hopeful that these very impressive early results with very well-tolerated drugs will lead into an improved long-term outcome.

One important thing as you are using any of these treatments is how to monitor the patients. And this is very important because we're learning more and more and obviously we're changing our routines as we get more information. I mentioned that at the time of diagnosis every patient should have a bone marrow and should have all the blood tests and get a chromosome analysis and probably a PCR test. When you're at the initial steps of therapy, monitoring the peripheral blood is very important to see if the counts, the white cell count, the platelet count, the hemoglobin, may go down a little too much. So we do them a little more frequently. Eventually patients get to a very stable count, most patients do, and in that setting you can make the frequency of these tests much less.

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DR. JORGE CORTES: Patients should be getting a bone marrow aspiration probably every six months until they get to a complete chromosome response, again meaning that there's no more Philadelphia chromosome in the bone marrow. And then the frequency of that will be decreased to every 12 and there are patients who have a very stable response, we do these bone marrows less and less frequently. But it is very important that they are monitored with a molecular test every three to six months to make sure that the disease continues well-controlled.

A FISH test could be used sometimes to replace or in addition to this chromosome test. Of course, that can be done in the blood and makes it more convenient than the bone marrow. It has some limitations that I don't have much time to explain, so you don't get all the information you get with the chromosome test. And also it is not as powerful as the PCR, so it should not replace the PCR, but it is a good action to continue following patients together with the other tests.

One important thing when we talk about these molecular tests is that we hear a lot of interest of patients to become what is started to be known as PCRU, meaning that your disease is undetectable in this test that we call the PCR. And of course, in any disease, in any cancer, we want to see as little disease as possible and hopefully no disease at all by any method of detection. So in that regard obviously it makes you feel better when you see the patients have this status.

However, it is important to remember that patients that have a complete cytogenetic response, again, no Philadelphia chromosome in the chromosome test in the bone marrow, they already do very well. If the molecular test is very low, within that group of patients, it may improve the outcome a little bit more, so there is a small increment of benefit. But there are patients who do not get to be undetectable. They still may have a very good long-term outcome and most patients, the greatly overwhelming majority of patients still do. So I think it is important to remember that, the way I explain this to my patients, is that I consider the molecular response a measure of success. Yes, I do want to get to the lowest value as possible on these tests and hopefully to become undetectable. But I do not consider it a measure of failure. Meaning a patient that does not have the Philadelphia chromosome any more, that has achieved a very good response, I monitor them closely, but that is by no means failure. And I think most of these patients can continue doing well, although they do again need to be monitored just like every other patient.

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DR. JORGE CORTES: Now one thing that could be important for achievement of this complete molecular response or PCRU is whether you could stop therapy on patients that become completely undetectable. And that's still a matter of debate. There are a couple of studies, one in France, one in Australia, which are starting to look at this in patients that have a complete molecular response, PCRU sustained for two years. And they have seen that when they stop therapy in those patients, in about half of the patients the disease will come back. Now usually what they found is that when it comes back, if they started Gleevec again, they respond.

Now I think this should be definitely considered as an experimental approach. This is not the way we recommend patients to be treated outside of a clinical trial. Today we should consider the treatment indefinitely.

The other thing that's important is to remember that in this study, it required that patients have PCRU sustained for at least two years and this is with a PCR that is very reliable, very high quality, very powerful. And that's a very, very important thing to keep in mind.

Another thing for monitoring that has become recently available is to measure the plasma levels of the imatinib. And we can do that in the laboratory. So that means we see how much Gleevec there is in your blood. And there's been some studies to suggest that if there is higher amounts of Gleevec in the blood, those patients tend to respond better.

And that may be a useful tool to complement whatever else we have. But we also need to make sure that we keep in mind that most of the decisions regarding managing a patient can be made by the usual monitoring, by measuring the response to therapy by paying close attention to any possible toxicities, and with that you can really manage patients without the need for the plasma levels. Now there may be isolated examples where measuring the plasma levels could add some benefit, but in general in my practice I very seldom use or need plasma levels and one should resist the temptation to use the plasma levels as the goal of therapy, but rather the elimination of the disease as the goal of therapy.

One thing that we have learned from the plasma levels, though, is the fact that the dose optimization is very important. We have learned that the patients who do the best are the patients who stay with the drug. We've learned that treatment interruptions appear to be much more common than we realized and there are many, many instances that patients have treatment interruptions for one reason

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DR. JORGE CORTES: or another. And we've learned also that these treatment interruptions do adversely affect the outcome. So that is very important to minimize these treatment interruptions, to optimize the doses, so that we can have the best probability of a long-term outcome.

Now this leads us to discuss some of the toxicity. And we do know that imatinib, that Gleevec, has been very fortunately a very well-tolerated drug. And it is important to keep that in mind because most patients can tolerate the drug well. Some patients will have side effects, but fortunately most of the side effects can be managed well.

What we call grade 3 or 4 side effects, which are the most severe side effects, are very uncommon fortunately. Now we do acknowledge that there are many patients that have these chronic, not very severe side effects, but persistent. There's fatigue and then there's some swelling, then there's some muscle cramps. Most of these side effects can be managed. And others, such as the fatigue, we're doing studies to try to understand it better and to manage it better, so that we can improve not only the long-term life expectancy, but also the quality of life. Obviously this is not as bad as when we used interferon, but you would like to see the patients feeling as good as possible for the rest of their life.

Now it is difficult to say when a patient should be considered intolerant to Gleevec and switch to one of the new agents because some of these low grade side effects could potentially be seen also with the new drugs, which are also very good, very safe, but there could be also some of these low grade side effects. So I think the most important thing is good communication with your doctor, to make sure that we make a good attempt at managing these side effects before we just consider changing therapies based on this.

Well, this leads me to the topic of failure. And as we mentioned earlier, unfortunately some patients do not have the response that we want to Gleevec and a few others may have the response we want, but eventually they can lose that response. And we know those patients then don't do as well and that's what led to the interest in finding new ways of treating these patients.

The first thing we did before there were new drugs available for this kind of condition is that we started increasing the dose of Gleevec in these patients and we know that some patients will indeed respond to dose escalation of the Gleevec, particularly those who at some point had a chromosome response. Those are more likely to respond to higher doses of Gleevec.

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DR. JORGE CORTES: However, then came the new drugs and I mentioned them earlier. One is called Sprycel or dasatinib and the other one is called Tasigna or nilotinib. And these drugs have been fortunately very, very good. We know that, for example, with Sprycel, among patients who failed Gleevec and failure would be considered when a patient either did not respond or lose their response to Gleevec or could not tolerate Gleevec, we get approximately 50 percent of the patients to have a complete cytogenetic response, completely become Philadelphia chromosome-negative. And these responses tend to be quite durable. That's in the chronic phase and the drug actually works well and is approved in all stages of the disease, accelerated and blast phase and even in a related disease that's called acute lymphoblastic leukemia with the Philadelphia chromosome. As you would imagine, the responses tend to be more durable when the patient is in the earlier stages than in the more advanced stages. In the more advanced stages, we're looking at combining this drug with chemotherapy or with other agents.

We've also known from several studies that when you compared the benefit of increasing the doses of Gleevec that I described earlier, to changing to, for example, dasatinib, the patients tend to have a better chance of responding to higher doses of dasatinib. So when a patient has truly failed Gleevec, we consider changing to a new drug. When we have what we call a suboptimal response, the dose escalation is a good consideration.

For Sprycel, one thing that's important is that initially this drug was approved at a dose of 70 milligrams twice daily. But the standard dose has changed in the chronic phase to 100 milligrams once daily. Because we've learned that this lower dose and this once daily schedule makes the side effects much less and keeps the response rate at least as good as the dose that was initially approved.

Sprycel is well tolerated. Some of the side effects that we see is that the counts may drop a little too much, the white cells, the platelets, just like with Gleevec. And one thing that has caught some attention with this drug is the possibility of having some fluid accumulate around the lungs, and this happens in some patients, probably up to 20 to 25 percent of patients, but fortunately this is very mild in the great majority of patients. Only a few patients really have recurrent problems that need to drain that with a needle or who just cannot take this medication.

I'll now move to the other drug, which is called Tasigna or nilotinib. And again, similar to Sprycel, this drug has been used in patients where there's been failure to imatinib and again, we see a complete chromosome response in nearly 45 percent of the patients, and these responses again tend to be durable.

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DR. JORGE CORTES: This drug, it's important to remember, has to be taken twice daily and on an empty stomach. And if you work around your sleep times, that's when I find it easier for most patients to take it. If you take it just when you wake up, you've been fasting already. And then by the time you get ready and get dressed and shower and all that, you let an hour go before you have breakfast. And then at night, so you have your dinner, wait a couple of hours at least, and then you can take your pill and then go to bed and that usually makes it easier to take.

The results also are very good. And one important thing, and we have data with Tasigna, but it applies to all these drugs, is the response rate and the tolerance are equally good in younger and in older patients. And I bring it up because today there should not be a reason why a patient, an older patient, should not be offered treatment with any of these drugs.

And this drug also works not only in the chronic phase, but also in the accelerated phase, and even in the blastic phase of the disease, although this drug has not yet been approved for the blast phase of chronic myeloid leukemia.

Nilotinib is also well tolerated. Again, the counts may drop a little bit, with sometimes an elevation of the bilirubin, elevation of an enzyme of the pancreas that's called lipase, but most of these are biochemical abnormalities that don't cause major problems.

One thing to remember with these drugs, particularly dasatinib and nilotinib, is that there's potential for effect in the rhythm of the heart and it's very important that we keep an eye on the potassium and the magnesium and probably do an electrocardiogram before we start, maybe about a week after you start. And with just minimum monitoring of the electrolytes, the overwhelming majority of patients will not have problems with these drugs.

There's a third drug that's still not yet approved that's called bosutinib or SKI606 and this drug also works in patients who failed Gleevec and it's also being tested as initial therapy.

Now one important thing to consider is for patients who fail Gleevec, it is important to remember that having the change of therapy, as soon as the failure is recognized, is important. And again, I do not mean by that not being PCRU or anything like that. But if your chromosome is still present after a long enough treatment, let's say at least a year, year and a half, and there is no complete chromosome response, it's better to start the change of therapy then, than wait until the counts start becoming abnormal, because the chances of response are better.

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DR. JORGE CORTES: And when Gleevec fails, that is when it is important to measure mutations. Because that's when it has some relevant use and in some instances it can help you select which of these drugs may be more beneficial.

Of course, we also need to remember that once Gleevec fails, the consideration of stem cell transplant is important, particularly for the younger patients that may have a better probability of a long-term outcome with this procedure.

And finally, just to mention that for those patients that either fail two or more of the available drugs, or for those patients that have this particular mutation that we call T315I, which is one where none of the drugs that I've described so far works, there are fortunately many drugs being developed, all of them in clinical trials, which are showing very promising results. Such as a drug called AP24534, another one DCC-2036, there's another drug that's an old drug that's called homoharringtonine or omacetaxine, and we've seen very encouraging results with many of these drugs, so I would encourage anybody who has this unfortunate situation to actively seek participation in these clinical trials because there are drugs available that can potentially help you. Of course, in that setting, transplant is important.

One important question, just to conclude, that I frequently hear as well, can we cure the disease with these drugs, how am I going to know that I'm being cured? And it's difficult to answer the question because we don't know how to define cure. For example, if you need to take the drug for the rest of your life, can you consider yourself cured or not? And I think if we can beat a cancer by taking a pill a day for the rest of life and the disease never comes back, I think it is something we can consider a cure or at least close to a cure.

Now whether we can get to the point where we can discontinue therapy and the disease will never come back, there is a lot of active investigation into this issue. And there are many things that are being used, for example, adding a little bit of interferon or vaccines and other things. And hopefully we're going to get to that point very soon. Although it probably takes you a few years.

But that brings me to my final topic, which is that participation in clinical trials then becomes very, very important. Because not only can patients get the best care possible when participating in clinical trials and have the option to receive the state-of-the-art, for example, the new drugs as initial therapy, the drugs available for patients who have the T359 mutation. But also the more we can include patients in clinical trials, the closer we will be to answering these questions and getting to be able to offer a cure for CML for all of the patients.

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DR. JORGE CORTES: So I am going to stop here with my presentation, so we can go to the question and answer session. And I'll send back the presentation.

CARSON JACOBI: Thank you so much, Dr. Cortes.

Before we open up the lines and the computer to start the question and answer session, there are several resources that I wanted to mention for all of you, our audience.

One of them is The Leukemia & Lymphoma Society's Co-Pay Assistance Program. This is separate and different from the Patient Financial Aid Program. The Co-Pay Assistance Program offers financial assistance to qualified CML patients, to help with treatment-related expenses and insurance premiums. And patients can apply online or over the phone with a co-pay specialist. And the Web site address is www.LLS.org/copay.

We also have a CML Tracker Tool. This is either in a booklet format or standalone interactive online tool. And this online tracker helps with you keeping on track with your medical appointments, drug therapy schedules, blood and marrow test schedules and results. And you can go online and the address to find the tool online is www.LLS.org/CMLtracker. Or you can call our Information Resource Center and they can assist you in ordering one over the phone.

I would also like to mention our partnership and our friends at The Max Foundation. Because we have several international participants, The Max Foundation helps patients who live internationally. And people living with CML and their families in any region of the world who need support services are encouraged to contact The Max Foundation. And their Web address is www.themaxfoundation.org.

So it's now time for the interactive part of our program. And before the operator gives instructions for you to enter the question and answer queue, I would like to remind you that because we have many participants on the line and we have several hundred on the computer, for everyone to benefit, if you can please keep your questions general in nature and Dr. Cortes will provide an answer general in nature. And I will alternate back and forth between our phone audience and our webcast audience. If you're on the phone, your phone line will be muted after you ask your question, so Dr. Cortes can respond.

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

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- OPERATOR:** To participate in the call by asking a question, please dial star-1 on your keypad. If you are joining us by web, simply click on Ask a Question, type your question, then hit Submit. 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 or click on Ask a Question, type your question, then hit Submit.
- CARSON JACOBI:** Thank you, Kayla. We'll take our first question from the telephone audience.
- OPERATOR:** Our first caller is Linda from Delaware.
- LINDA:** Hello, Dr. Cortes. I have a question about a side effect of Tassigna. You did not mention that another side effect possible is the lipase going very, very high. And I'd like to know when the lipase goes over two times the normal high, are there a lot that have this side effect and is it extremely harmful? The patient I'm a caregiver for has had leukemia over ten years, is doing pretty well on Tassigna, but that is a side effect. The FISH complete cytogenetic response is good and by FISH it's a complete hematologic response. But this is a side effect we're concerned about.
- DR. JORGE CORTES:** Thank you, yes, this is the pancreatic enzyme that I was mentioning, the lipase, that's an enzyme that comes from the pancreas. And we do see that frequently, well, about 10 to 15 percent of the patients have a significant elevation. And it happens less frequently with the other drugs, but it happens also with some of the other drugs we have.
- Here it's very important, fortunately, most of the time there is no evidence of a pancreatitis, which is good. So it tends to be just an asymptomatic elevation. So it has to be followed closely with your doctor to make sure that there is no other symptoms. And most of the time the way we manage this is by seeing if we need to hold therapy temporarily and sometimes we need to adjust the doses, maybe cutting down the doses, to try to minimize the symptoms. And many times it responds to that and patients can continue with therapy.
- Now if the elevation is not very high, some patients can continue therapy. But that's obviously something that depends on the other features of the patient and how high the elevation is. That's something that needs to be discussed with your doctor to make sure the treatment can be continued safely.

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CARSON JACOBI: Thank you, Linda, for the question.

We'll take a question from our webcast audience. Pamela asks, "Should CML patients be vaccinated for the swine flu and is it safe?"

DR. JORGE CORTES: That's a very important question and a very timely one. We, of course, know very little about the swine vaccine. It's a vaccine that is just now starting to appear in clinical trials. And we know from recent reports that normal individuals can have an immune response to the vaccine. We'll have to see how protective that immune vaccine is.

We know a little bit more from the regular vaccines, so I'm going to use that information. And we know that probably about half of the patients with CML can have an immune response to the regular flu vaccine and they don't seem to have problems. So you would expect that there will be some protection.

Now only about half of the patients that have been investigated have shown to have a good immune response.

I still think that probably, particularly patients that have a well-controlled disease, that are in the chronic phase, who have responded to treatment, who are very stable, we believe that it's probably going to be safe to administer the vaccine. Certainly the regular flu vaccine. The swine vaccine, we'll continue following the information, but it's probably going to be about the same guidelines. And we don't know anything about long-term side effects for patients with CML or normal individuals, so we'll have to follow that very closely. But it is something that's going to have to be very important to follow closely with your doctors. But in short, I would say that it is likely that we will be able to give it to patients with CML that are well-controlled, that are very stable, with a good response.

CARSON JACOBI: Thank you, Pamela, for the question. We'll take our next question from the telephone audience, please.

OPERATOR: The next question comes from Isabelle in Indiana.

ISABELLE: Dr. Cortes, my doctor in Indianapolis has emailed you prior, but things have progressed and I'm concerned. I have a high intolerance to Gleevec and Tassigna and now I've tried Sprycel and my platelets are down right now, so I'm waiting for them to go back. But I've had no real side effect problems with the Sprycel except the blockage, not being able to go to the bathroom, that's no biggie, I can handle those things.

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ISABELLE:

Real quick, I'm a, and this is not the right word, I'm a low-wgrade level of CML. I took the Gleevec for four weeks and went totally back to normal, at 15 percent actually CML. Then I stayed off of it for like two or three months and the doctor went away on vacation. And what happened was that my CML percentage dropped again to 5 percent. And all my blood levels were good, all my counts were great. And so this newer doctor has told me that I have this really good bum of it, to have it at all. My question to you is because I suffer from nocturnal leg cramps and huge indigestion problems, lower respiratory problems due to the fact that I have liver disease as well as diabetes and suffer from nocturnal leg cramps that just become so excruciating I had to get off Gleevec and Tasigna thus far. I just couldn't do it another minute, it was too painful. And I need to know should I be doing a drug on trial, perhaps come and see you? Because I really feel like I could still reach remission. And in that, my doctor says the longer I wait, the less chance I have to get to remission, the first doctor. He was at IU Simon Center in Indianapolis. And he did write you. But he told me that the longer I wait, going through all these trials and tribulations with these drugs, the lesser the chance I have to get to remission at all. I've reached hematologic, but that's not where I want to go.

CARSON JACOBI:

Thank you so much, Isabelle, for your question. Dr. Cortes?

DR. JORGE CORTES:

Thank you. We described that there were some, fortunately a small percentage of patients, but patients who may have this situation where they may not tolerate, or some that may not respond to any of the three drugs. It is hard for me to answer in an individual case, but in general patients who are having side effects, there are two main things to do. One is do the best management of the side effects possible. Some patients, the side effects will respond to, I don't know, the muscle cramps can respond to tonic water and quinine, things like that. And two, to use dose adjustments. If it is a disease that is very responsive to therapy, sometimes we can lower the doses a little and still get a good response, so that is another tool that one has to try to make sure that the patient can stay on treatment. All these things have to be discussed with the doctor to see what are the options.

If none of that works, then there are these new drugs that we were discussing, where some patients have had that situation where they don't respond to any of the drugs or they cannot tolerate any of the drugs, and fortunately some patients do benefit from these new agents and that's something that could be considered. So depending on the specific scenario, all of these options are available.

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CARSON JACOBI: Thank you, Isabelle, for the question.

We have a question from our web audience, it comes from Pamela. She asks, "What are the best medications, one for acid reflux indigestion for CML patients, and anxiety for CML patients? Those that are least likely to interfere with Gleevec."

DR. JORGE CORTES: Well, part of that depends on the other characteristics of the patient and so in general terms, and all of this has to be individualized for each patient. Still for acid reflux, if it is a very significant problem, it is probably worthwhile having an opinion of a gastroenterologist and see if there may be other measures. Sometimes there could be an infection by a parasite that we call *Helicobacter pylori*, which responds very well to specific intervention with some antibiotics. So if that is the case, that has to be addressed and that solves the problem in the majority of patients. So what the best treatment would be depends on the situation.

Now we know that taking some of the antacids, particularly things that decrease the acid production in the stomach, may interfere to some extent with the absorption of some of these drugs, so it has to be used with caution and probably separated from the time where we use the Gleevec or the other drugs as well.

The same thing for anxiety. There are so many reasons why a patient can have anxiety that there are many ways to manage that. And that is probably best individualized to the specific situation.

CARSON JACOBI: Thank you for the question. We'll take our next question from the telephone audience, please.

OPERATOR: The next question comes from Fran in New York.

FRAN: Hi, everyone, and Dr. Cortes. I wondered if you could say a few word about the use and/or overuse of Aranesp® with CML patients on Gleevec to raise hemoglobin levels and what is considered a safe level to achieve.

DR. JORGE CORTES: Sure, yeah, that's an important topic because many patients may have some level of anemia with the use of any of these drugs, Gleevec, Tasigna, Sprycel, they all can cause some anemia. And of course, the first thing is that not every patient that has an anemia, particularly if it's a minor anemia, needs any intervention, whether these drugs may work or not. So that has to be kept in mind. But many times this can just be followed.

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DR. JORGE CORTES: For those patients that have a more profound anemia or one that is clearly causing symptoms, then these drugs have been used. And you mentioned Aranesp and the same can be said about Procrit®. And these drugs have been used and we know that they work. They can improve the anemia in many patients. There have been concerns because there were some cancers in which studies have suggested that patients who take these drugs with their chemotherapy may actually have a worse outcome, meaning that the cancer may recur or they may do so sooner. So that has created a lot of concern about the use of these drugs in cancer patients.

Also in myeloid diseases and CML, it's a chronic myeloid leukemia, so it's a myeloid disease, there has been the concern, that at least in the laboratory, they can stimulate, these drugs can stimulate the growth of the leukemia.

So I think these drugs have to be used with extreme caution. We use them in some patients and there is no evidence available at the moment that the patients who take these drugs have any worse outcome, again provided they have anemia, they have an indication. But it is something that has some potential risks, at least from the data we know from other cancers, and it has to be discussed very carefully with your doctor for each individual patient to see all the risks and benefits.

CARSON JACOBI: Thank you, Fran, for your question.

We will take our next question from our web-based audience. It comes from Jane and she asks, "Can you talk a little bit about Sprycel and its success as second option after Gleevec?"

DR. JORGE CORTES: Sure. We mentioned this briefly and it's been fortunately a very, very good drug in patients who failed Gleevec, as I mentioned. About half of the patients will get a complete chromosome response and these responses tend to be durable, meaning the drug is relatively new, so we only have about two to three years of follow-up. But most of the patients who respond have maintained a response through this time.

So it's an excellent drug. It's overall very well-tolerated. There are some side effects and we mentioned some of them during the presentation. But most patients can take it very well. So for patients who fail Gleevec, that is one of the options, Tasigna being the other, that should be considered. And it can be very valuable and that's why we are starting to use that in clinical trials, even as initial therapy, to try to improve the long-term outcome.

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CARSON JACOBI: Okay. We will take our next question from the telephone audience, please.

OPERATOR: Your next question comes from the line of Brian in Utah.

BRIAN: Hi, Doctor. I am wondering if you could just briefly talk about the expensive nature of Gleevec and if you see any relief from that in the future.

JORGE CORTES: Wow, you just put me in the middle of this debate in Congress. It's evidently a major topic because we're getting, not only for this disease, but for many diseases, cancers and others, we are getting obviously better and better agents, but unfortunately the cost is also quite high.

We know that there are some assistance programs that can help. Some of them come from the drug companies themselves, some of them from other organizations. There was some talk about the excellent program that The Max Foundation has. But of course, we're all interested in seeing that hopefully the cost of these drugs may be more accessible to everybody, particularly those who may not have insurance.

It is a difficult topic because there are many reasons why the costs are so high. And I think it is difficult to solve them with just one action. But I think at least it's good to know that there are a lot of initiatives and a lot of interest in getting this solved and hopefully we will see some things happening soon.

CARSON JACOBI: Thank you, Brian, for your question.

We will take our next question from the web-based audience and this question comes from Erin. She asks, "How long will my husband have to be off Gleevec before we can bank his sperm and/or attempt to get pregnant? What is known about the effects of Gleevec on sperm and sperm development?"

DR. JORGES CORTES: That's a good question and one that comes frequently. And the data for male patients that are in this situation is, in animal studies, and we frequently have to refer to that, we know that what happens with the male animals when they're exposed to Gleevec, and particularly at very high concentrations, is that there may be some infertility. But it doesn't seem to affect too much the quality of the sperm, but probably the count. And if they are able to actually father babies, then the babies don't seem to have problems.

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DR. JORGE CORTES: Now in patients, there have been a couple of reports already showing that the babies that are born from fathers who were taking Gleevec, and also starting to come with some information also with Sprycel, so the babies that are born from fathers who were taking these drugs at the time of conception, there doesn't seem to be much of an evidence of a problem. And there is probably not a firm contraindication for this.

I still think that thinking about banking sperm is a good idea, just to increase the safety. And there's no firm guidelines and we're still debating about this among people. But usually I would say that just a few weeks would be probably enough to make sure that there's no possible problem with the sperm. Although again, there's no formal contraindication for a father to have a baby.

Of course, one has to be aware of the risks and follow the pregnancy closely, to make sure that the baby is developing well.

CARSON JACOBI: Thank you. Kayla, we'll take our next question, please, from the telephone audience.

OPERATOR: Your next question comes from Francis in North Carolina.

FRANCIS: Thanks, Dr. Cortes, excellent presentation. As you know, many of the labs are now converting to the international scale for reporting the PCR levels. I find these very difficult to interpret and I don't find that the labs are very clear in their reporting. I wonder if you could recommend any literature that was in layman's terms, which would allow one to correctly interpret these results. Especially due to the fact that some of the labs have converted recently and many patients had their original PCR test done before the international scale was instituted. Thank you very much.

DR. JORGE CORTES: Thank you. That's a very good point. The conversion to the international scale is very useful because it allows you to interpret the results that come from different laboratories better. If you get your hemoglobin measured in different laboratories, the results you get in one laboratory you know will correlate very well with what you get in a different laboratory. We all express them the same way, we all use the same scales. But that's not the case yet with the molecular test, that's why the international scale is trying to come up with a conversion factor, so that we all refer to a common denominator. And if you get the results, for example, at M.D. Anderson, we can convert to that common denominator and then the next time you have to get it somewhere else, you can convert to a common denominator.

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DR. JORGE CORTES: Now unfortunately, not all of the labs have even attempted that conversion to the international scale and if they have, sometimes they don't report that. So the first thing you need to do is check with your doctor to make sure that whether the results you're getting refer to the international scale or not. Because it's become increasingly desirable to have that being done. And sometimes you may not get it in the report, but you can get it by just asking the question.

When you get to the international scale, then you know that when you get to less than 0.1, that is what we call a major molecular response. So it makes it very easy to follow.

In terms of literature to read in lay terms, of course, The Leukemia & Lymphoma Society has very good educational tools in these and other aspects, which I think you can refer to. And I'm sure you're going to find it very helpful.

CARSON JACOBI: Thank you, Francis.

We will take our next question from our web audience. And the question, Dr. Cortes, is about pediatric CML. "Do you recommend a BMT, bone marrow transplant, or to continue with Gleevec if it is working?"

DR. JORGE CORTES: Well, that's a very good point and I think that if a patient has started already Gleevec and the response is very good, I think it is worth considering. Now we know that probably the pediatric patients may have some—that the Gleevec may affect the growth to some extent, so they may slow the growth curve. But we don't know that there are any problems long-term with the Gleevec. So if the patient is responding well, I would probably continue with the Gleevec. But one thing is that certainly for young patients, very young patients, if they have a very good donor, I would be very intolerant to any lag in the response rate. So that's a patient that's particularly critical to follow very closely and particularly during the first year or so, to make sure that the response goes as well as you want. If that's the case, perfect. If that is not, well, then consider quickly the change to a transplant. So I think the answer to the question depends a lot on what kind of response you're having.

CARSON JACOBI: Thank you for that question. Thank you all for your questions. Our program has come to an end.

Please help me thank Dr. Cortes. We are so grateful he has donated his time to us today. And again we thank him for all the work that he does every day in supporting families touched by cancer.

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CARSON JACOBI: We would also like to thank again Novartis Oncology for their support.

We hope that some of your questions were answered and that the information will assist you and your family in your next steps. If your questions weren't answered and you would like to follow up with the Information Resource Center, I will provide that number in just a moment.

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

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

OPERATOR: Thank you for participating in today's conference call. You may now disconnect.

END