CML–Living with a Chronic Disease | April 17, 2013

Speaker: Jorge Cortes, MD

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

Slide 1: Welcome & Introductions

OPERATOR:
Hello, everyone, and welcome to *CML–Living with a Chronic Disease*, a free telephone/ web education program. It is my pleasure to introduce your moderator, Mabel Maia of The Leukemia & Lymphoma Society.

MABEL MAIA:
Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you and a special thanks to Dr. Cortes for sharing his time and expertise with us today.

We are proud to offer this program in collaboration with Abrale and Alianza Latina of Latin America. We would also like to acknowledge and thank Novartis Oncology and Bristol-Myers Squibb for their support of this program.

Today we are simultaneously interpreting our program into Spanish. If you'll notice, I am speaking a little bit slower today and also Dr. Cortes will be speaking a little bit slower, to allow for simultaneous interpretation.

We have close to 1,200 individuals participating from all over the world and because of our simultaneous interpretation, we have a large audience participating from Spain and other Latin American countries. On behalf of LLS, thank you and welcome.

Before we begin, I would like to introduce The Leukemia & Lymphoma Society's President and CEO, John Walter, who will share a few words. Thanks, John.

JOHN WALTER:
Thank you, Mabel. I would like to add my welcome to the patients, caregivers and healthcare professionals on the program today, participating in both English and Spanish.

All of us at The Leukemia & Lymphoma Society believe we are living in an extraordinary moment. Our mission is to cure blood cancers, including leukemia, lymphoma, myeloma and to improve the quality of life for patients.

Since 1954 LLS has been a driving force behind almost every treatment for patients with blood cancers and we have awarded more than $875 million to fund blood cancer research.

Our commitment to pioneering science has contributed to an unprecedented rise in survival rates for people with many different blood cancers. An important part of our mission is bringing you the latest information about advances in treatment for your blood cancer, so you can work with your healthcare team to determine the best options for the best outcomes.

Until there is a cure, LLS will continue to invest in research, patient support programs and services, that improve the quality of life for patients and families.

We are fortunate to have as our presenter today our friend, Dr. Jorge Cortes, one of the nation's leading experts in CML. We appreciate his dedication to supporting the mission of The Leukemia & Lymphoma Society through his research and his care of patients living with CML. I would like to personally thank him for providing us an important update on CML, Living with a Chronic Disease.

JOHN WALTER:
Thank you and I'll turn the program back over to Mabel.

Slide 2: Jorge Cortes, MD

MABEL MAIA:
Thank you, John.

I am now pleased to introduce Dr. Jorge Cortes. Dr. Cortes is the D. B. Lane Cancer Research Distinguished Professor for Leukemia Research. He's also the Deputy Chairman and Section Chief of AML and CML in the Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston, Texas.

Dr. Cortes, we are so privileged to have you with us today and I now turn the program over to you.

Slide 3: CML–Living with a Chronic Disease

DR. JORGE CORTES:
Thank you very much and welcome, everybody, to this program. For those of you who speak Spanish, bienvenidos.

And we are going to talk about CML and I think the title is telling us where we are in the treatment of chronic myeloid leukemia.

Slide 4: Survival in Early Chronic Phase CML
In the first slide, what you can see is the expected survival of patients that are diagnosed with chronic myeloid leukemia. What we've seen since the 1960s, which is when we first recognized that there was this unique chromosomal abnormality that we call the Philadelphia chromosome, and then through different ages until today, where you see that the life expectancy by five years, more than 90% of patients are going to be alive.

There's been some analysis that suggests that for the majority of patients who have received adequate treatment, the life expectancy is probably very close to that of the normal population. So this is a disease that we've made great progress with. We have the tools to conquer this disease. And therefore we do have the ability to transform this deadly disease into a chronic disease, where patients are going to live with it, with their medication. And it is very important to understand what that means and what are the steps that we need to take to make sure that patients have such good outcomes.

Slide 5: Some Important Topics in CML 2013
So the next slide, what I'm showing you is some of the important topics in CML today that are the things that we're trying to do to improve the life of the patients and the probability of the patients having very long survival and being able to enjoy a normal life and have their life expectancy match that of the general population. It has to do with the treatment that we use initially, it has to do with the evaluation of response, how we assess the responses, the timing of the responses. It has to do even with our initial thoughts about can we discontinue treatment. It has to do with how we manage those instances where the treatment is not as good as we would like it to be. And it has to do with the importance that clinical trials play in all of these. It has played a great role in where we are today and it still has an important role on where we need to be.

DR. JORGE CORTES:

Slide 6: Results with Imatinib in Early CP CML

Now let's review some of this information. This slide now shows you the data that we have from the study that was called the IRIS trial. This was the first study where a tyrosine kinase inhibitor was used to treat patients with chronic myeloid leukemia as their initial treatment. That drug that was started in the year 2000, 2001, the drug was imatinib or Gleevec® and what we have is an eight year follow-up. And we know that the results were very good. A large percentage of patients achieved a complete cytogenetic response and that translated into most patients being able to be alive and, importantly, alive and well. That's essentially what event-free survival means. That means that the patients are alive and they do not have any recurrence of the disease, they have not lost the response, etc.

These are eight year follow-up. Unfortunately, this study's been terminated now, so we will not have longer follow-up, but there other studies that will provide that from our institution and other large institutions and comparative groups, that will allow us to answer important questions as to what happens when you take these drugs for ten years, for 15 years, for 20 years. Because nowadays we are having patients living longer and importantly, we are diagnosing patients younger, who are looking to live not just eight to ten years, but much longer than that.

Slide 7: IRIS 8-Year Update

Now in the next slide, I am presenting the data from this study in a slightly different way. We know, and I'm going to get to that a little bit later, but we know that the minimum that we can accept in a patient that is diagnosed with chronic myeloid leukemia is to achieve a complete cytogenetic response. What that means is that when we do an assessment and look for the Philadelphia chromosome in the cells in the bone marrow, we do not find it any more. And when you look for that as your minimum favorable response, we know that on this study and when you use imatinib, about 15 to 20% of patients never get that response. Some others get that response, but eventually lose the response. And then there are some patients who just completely cannot take the medication, they have serious side effects that do not allow them to continue taking the medication. So when you look at it that way, you realize that at least a third of the patients do not have the favorable endpoint, the favorable outcome, that we would like to see on every patient.

So that triggered a number of studies to try to see those great results, how can we make them even better. Well, fortunately, we do have ways to make these treatments better.

Slide 8: Nilotinib vs. Imatinib

The next slide shows the analysis of the use of the newer drugs we developed, what we call the second generation tyrosine kinase inhibitors. And we started initially using those in patients who have not responded well to imatinib. But then we started using them as the initial treatment for the disease.

What I'm showing you on this slide is the data with nilotinib or Tasigna® and comparing it with imatinib or Gleevec. In this study, we can see that patients that started treatment with nilotinib, they have a much better probability of getting a good response, both the cytogenetic response, the chromosome response, and their molecular response. These are deeper responses that show that there is much less disease left.

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Importantly, this correlates with fewer patients, a lower risk of transforming into the more advanced stages of the disease. And that is very, very important because these advanced stages of the disease are a lot more difficult to treat.

Slide 9: Dasatinib vs. Imatinib
The next slide shows a similar study with another one of these drugs that was also initially used after patients had failed imatinib. And then this study shows the use as initial treatment for the disease. That is dasatinib or Sprycel®. In a similar study comparing head to head to imatinib, you see essentially the same thing. Many more patients get a good response, a cytogenetic response, a molecular response, and fewer patients transform to the accelerated or the blast phase.

So with this we know that we can get more patients to achieve a good response, fewer patients to get to the more difficult stages of the disease.

Now one of the important things that we've learned is that it is very important to get a response, but it is also very important when you get the response. Because we've learned that the earlier the response is, the better the chances of the patients doing well. And this happens, this separation, happens as early as three months.

Slide 10: 3-Year EFS by Molecular Response at 3 Months
In the next slide I'm showing you a summary of three studies. The first study is called the ENESTnd is the study I showed you a couple of slides ago of Tasigna compared to Gleevec. The next study is DASISION, which is the study that I showed you in the previous slide of Sprycel compared to Gleevec. And a third study is called the BELA study, of bosutinib, I'm going to talk about these drugs later, compared to Gleevec.

And what we've learned, as I said, is that as early as three months you can determine which patients are doing well and which patients are starting to lag a little bit behind. So if we do, for example, an analysis by PCR, which is something that every patient should have at this time points and we see whether their results show less than 10% or more than 10%, and this should be on what we call an International Scale, so that this value applies.

You can see that the patients that have a good response, which is the patients that have 10% or less, they have a much better chance that by three years they're going to be alive and they're going to still be in remission. There is about an 8 to 25% difference in the probability of being alive and well when you have a good response.

Slide 11: Molecular Response at 3 Months by Therapy
Now on the next slide, what I'm showing you, is how likely is it that you're going to have a bad response, that you're going to have more than 10% in these transcripts. So this is a bit of a complicated slide, but I've highlighted in yellow the area of interest. What I marked in yellow in these studies are the patients that are not having the best response that we want at three months.

The blue bar, the hatched blue bar, represents the patients treated with Gleevec. As you can see, about a third of the patients treated with Gleevec do not get the response we want as early as three months.

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When we start the treatments with the newer drugs, with Tasigna or with Sprycel, you see that far fewer patients get these poor responses. Only about 10 to 15% of the patients. So we know that these early responses are important and we can get them better if we use the newer drugs.

Slide 12: 3-Year OS by Molecular Response at 3 Months
Now on the next slide I also want to emphasize one important point. I showed you earlier that there is a difference in the probability of being alive and well. Now this difference I'm showing you, shows the probability of being alive. So you may have lost your response, but you're still alive because few patients transform to the advanced stages of the disease with these drugs. So there is a smaller difference between the good responders and the poor responders at three months in terms of the probability of being alive.

What this means is that a response as early as three months can let the doctor and the patient know how things are moving along and it's a good way of number one, reassuring that things are moving in the right direction, so that we're going to have a good response in the long term, or a way to say well, maybe we need to pay a little bit more attention and see if there are things that we can do different, that we can do better.

Slide 13: Early Response to TKI
Now what happens, if you happen to be one of those that are having a bit of a slower response, is there anything you can do about that? Well, there is. And the next slide shows what happens when you check again on those patients three months later. And as you can imagine, if you check on the patients who are not responding well at three months, you check again three months later, so that's six months from the start of treatment, some patients will have achieved a good response, some patients may still be lagging behind.

So in this slide what I'm showing you is, on the column that is marked MCyR, those are patients that by six months have cut off. They've now achieved a good response, even though they were a little behind at three months, and those patients have a very good outcome, even as good as if they had responded well at three months.

Now the patients that are still lagging behind, those patients are having lower probability of having a good response in the long term.

Slide 14: Early Response: What to Do?
Now what does all of this mean? So on the next slide I am trying to summarize this information, which may be a little complicated. What this means is, in summary, that an early response is very important. And some of the messages for this is one, is that it is very important that we monitor very closely, from the very early time points, and continue doing that throughout the therapy. That is the way we can detect whether a patient is having the response that we want, whether a patient is lagging behind, and whether we need to do something about it.

Importantly, these early responses correlate with the response duration. More than with the probability of transformation. Meaning taking these drugs already kind of cuts greatly the chances of the disease going

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to the more advanced state. But it may affect the probability of losing the response. And of course, we never want any patients to even lose the response.

Now it's also very important to remember, I showed you, that most patients that are lagging behind at three months can still do well in the long term. So that's an important message that I want to send, that this is not a hopeless situation at that point, but it is just a warning situation and we always want to be looking at these warnings because that is when you can think about things to do. Do we change therapy at three months? Right now we don't have any data that that's what you need to do, but you definitely need to make sure that you check again at six months. You also need to make sure that any factors that may be affecting this slower response are addressed. Could it be that we're not taking the medication as we should? Could it be that we are using too many interruptions because of side effects? Should we be managing those side effects? Should we be doing something else? So these are the kind of things that we need to be paying attention from the early time points and always throughout the therapy.

Now since I'm talking about these responses, I also want to emphasize a couple of things that have to do with the way we monitor patients.

Slide 15: IFNα in CML Survival by CG Response
In the next slide I'm showing you data from the very old day. This is from the days that we were treating patients with interferon. And this slide shows the probabilities of the patients staying alive, according to the response that they have by chromosome analysis, that is the cytogenetic response. And the yellow curve represents those patients that achieved a complete cytogenetic response. As you can see, that is associated with a very good chance of being alive ten years later. Eighty percent of those patients are alive ten years later. That is why, as I mentioned earlier, that's the minimum we should accept. Those are the patients who are likely to do well in the long term.

Slide 16: IRIS-EFS by Molecular Response with Imatinib at 18 Months
Now in the next slide, we've also learned that if you now take patients that have a complete cytogenetic response, and now you start looking for even deeper responses, we have better tools for monitoring, we have better treatments, so we can get deeper responses beyond that complete response.

You can see, if you look at the curves that are white and red, both of those patients have a complete cytogenetic response. But the white, which have a deeper response by molecular analysis, what we call a major molecular response or MMR, those patients have a better probability of being alive and well if they have achieved that response by18 months.

Now throughout the therapy we keep emphasizing the importance of continuing monitoring the patients. And we are interested in trying to see if the patients can get to what we call a complete molecular response or an undetectable molecular response. Many of you call it a PCRU, you know, all of these terms are potentially showing you the same, which is we do not see the disease even by the PCR.

Slide 17: Molecular Response in CML
Now what does that mean? Well, on this next slide I'm showing you some information about what does having undetectable disease mean. And there are many modalities of treatment that have been used, from Gleevec at standard dose, to higher doses of Gleevec, to Tasigna or Sprycel. And this is some

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analysis that we've done from our patients that we've treated with all of these different types of therapy, and if you look at this pie chart, it tells you how many patients fall into each one of these categories of molecular response. All of these patients have a chromosome response. Now how deep is their molecular response? And the blue part of the pie represents the patients that are completely undetectable, as the PCRU, the CMR, however you want to call it. As you can see, the newer modalities of therapy give us more patients to get to these deeper responses. They get, about 30% of patients by three years, have been completely negative by PCR.

Slide 18: Molecular Response in CML
Now the question is, what does that mean? Is that of value to the patient? So in the next slide I am showing you the probability of being, again, alive and well, depending on whether you have achieved this response or not. Whether you have achieved an MMR or a deeper molecular response or completely undetectable.

As you can see, the deeper the response, the lesser the chance that the patient will eventually lose their response, so that is very important, to get to that point, seems to be important in terms of maintaining that response.

Slide 19: Molecular Response in CML
Now very importantly on the next slide, it doesn't affect the probability of transforming to the more advanced stages. It doesn't affect the chances of being alive. And the reason for this is because all these patients already have a complete cytogenetic response, and I've emphasized that. We need to get to a complete cytogenetic response. That's the very important, first and most important goal.

Now beyond that, getting a deeper response can get you to have a lower probability of losing the response, but as long as you get to a complete cytogenetic response, it's very unlikely that you go to a more advanced stage or that you will die from the disease.

Slide 20: So What Do We Get?
So in summary, on the next slide, what we get is if you control the counts only, which is what we call a CHR, or complete hematologic response, the symptoms improve, but that doesn't benefit the patient in the long term, meaning they don't live any longer. When you get to a complete cytogenetic response, that is when patients really have turned an important corner and they are much more likely to live longer, perhaps a normal life expectancy. When you get to the deeper molecular responses, you start getting an improvement in the probability of having these durable remissions and less of a chance of eventually losing the response.

Now when you get to the deepest response, the complete molecular response, there has been the discussion about treatment discontinuation. So let's talk a little bit about treatment discontinuation. And as you noticed on my first slide, I talked about the voluntary and the involuntary treatment discontinuation.

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Slide 21: TKI Frontline Therapy in CML
On the next slide I'm showing you a summary of how frequently patients have discontinued therapy within the first two to three years in these large studies that have compared the new drugs with the old drug Gleevec. And as you can see, about 30% of patients, sometimes a little bit more, have discontinued therapy with these early time points. And that seems to be like a big number. We emphasize a lot that these drugs are well tolerated, but we have here about a third of the patients that are stopping treatment. So why are we having to stop treatment in some of these patients?

Slide 22: Factors Influencing Early Discontinuation of 2nd Generation TKI
So in the next slide I discuss some of the factors that make us have to stop the treatment in some patients. Of course, sometimes adverse events are an important reason to discontinue treatment. Now here I think one important thing that we need to acknowledge is that many of the adverse events can be managed. Sometimes dose adjustments can be done, sometimes management of certain symptoms can be done. And I think it is very important that some of that is done before we just change to another drug. It is a great thing that we have other drugs, but we don't want to just burn all our bridges before trying one, because sometimes we could go through every treatment option and then we'll have nothing to do and we need to recognize that all of these drugs have some side effects. Manageable, most of them. But it is possible that the other drugs also will have side effects.

Now we also change treatment when drugs are not working well, therefore the importance again of monitoring the patients all through the course of therapy.

Now I was alluding a little earlier to the fact that we have too many options, is probably making us think quickly about changing therapy. And that's an important tool we have. We do have other treatment options and if a patient really cannot take one drug, we should consider looking at the other drugs. But I also try to always see if there is any way that we can manage the adverse events, adjust the doses, etc., so that we can try to stay with one drug, especially if it's working, and try to get the patients to feel better and get the benefits of a drug that is beneficial.

Slide 23: Imatinib Treatment Discontinuations
Now we also are interested in can we at some point just stop treatment in the patients who are doing very well. So in the next slide I approach this question. And there have been some studies that have looked at this. The largest experience comes from France, in a study that's called the STIM trial. And in that study patients that had achieved a complete molecular response, that had been sustained for at least two years and assessed with a very, very sensitive test, and that's very, very important, that these criteria all are met, then they offer the patient to stop treatment. What they found is that two years later, 40% of patients, they had not lost their response. Now, of course, 60% had lost their response. Fortunately, when they lost their response, it shows that the PCR became positive and in the majority of them, when they restarted treatment, the molecular test became negative again. So this is important because it tells you that perhaps in some patients we can do this.

Now of course, this is perhaps not the optimal outcome that we want because number one, only about 40% of patients can meet the criteria of the complete molecular response, sustained for two years, with

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that 5-log sensitivity. And of those 40%, only about 40% can remain in remission. So 40% times 40% is 16%. We need to improve that. But at least it tells you that it's possible and we need to move there.

Now very, very important. Treatment discontinuation should never be done just spontaneously. This has to be discussed with the physician, with very proper follow-up, always in the context of a clinical trial, because you want to make sure that there is the adequate setting to consider treatment discontinuation, and the adequate follow-up, so that we don't risk making something that is looking good into a progression to an accelerated phase or a blast phase that can make things a lot more difficult.

Slide 24: Predictive Factors for Sustained Undetectable Transcripts
Now we know that the certain factors that make it more likely that you will be one of these patients that get to these deep responses. Curiously, older patients seem to have a better chance of having these sustained complete molecular responses. And it looks like the older patients tend to be paying more attention to their drug and taking their drug on time, etc. Taking the newer drugs is another factor, Tasigna, Sprycel, they tend to be – more patients who get to that, to that deep response. And also the patients who get the responses earlier tend to be the patients who get to the sustained responses in the long term.

Slide 25: Adherence to Imatinib
Now one important factor that is also very critical in the probability of achieving these deeper molecular responses is staying with the medication. This study, for example, from England, they looked at how much of the drug the patients were taking and these were patients that had been receiving Gleevec for at least two years. And what they found is that patients that had missed at least 10% of their doses or more, none of the patients actually had achieved a complete molecular response. So it is very important even a few pills that you miss here and there, it could get to be 10% of the pills that you are supposed to take, can be an important factor that prevents from getting these best responses.

Now there are reasons why patients miss these doses. Sometimes it's because of side effects that have not been managed. So very important is if there are things that are preventing a patient from taking the medication, whether it's access to the medication or side effects or any concerns, these have to be discussed with the doctor because in many cases there are things that can be done about that and that we should help our patients be able to maintain the treatment adequately to get the best response possible. So always, always talk to your doctor about any of these issues.

Slide 26: Bosutinib in CP CML
The next few slides, I just want to talk about three new options that have come recently in the U.S. and in other countries, they're starting to be available as of the last year.

One of them is called bosutinib or Bosulif®. This is a drug that is like Tasigna or Sprycel, drugs that are more potent than Gleevec, and that they work when Gleevec has stopped working. And in this study, patients who had received Gleevec, you see that about half of the patients can respond very well to Bosulif. It is an important new drug. All of these drugs have slightly different side effects, different properties, schedules, whether you take them with food or not. So one good advantage of these is that having different options allows you to discuss what may be the best fit for a patient, depending on the

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characteristics of the disease, the other problems that a patient may have, other comorbidities, other diseases, etc. So it's important to discuss all the treatment options to see what may be a better fit.

Slide 27: Ponatinib Phase 2 Study
The next one is ponatinib. Ponatinib or Iclusig® is a drug that importantly is effective against the mutation, T315I, where none of the other drugs that I have talked about so far works. But in addition, it works on patients that have other mutations or no mutations. And in this study where patients had received two or three prior therapies, we still saw that about half of the patients had a complete cytogenetic response. So it's a drug that's also very well tolerated, also oral, and again gives us yet another option for managing patients who have not responded well to prior therapy. And there are studies ongoing now to look at the use as initial treatment for the disease.

Slide 28: Omacetaxine for CML CP
And finally, a drug called omacetaxine. There may be somebody in the audience now that's coming from the days of interferon and in those days there was a drug that we called homoharringtonine, or there may be somebody in the audience from China where this drug comes from. Well, omacetaxine is a drug that is not a tyrosine kinase inhibitor like the other drugs. And it's a drug that's given as an injection and it can help some patients that have not responded well to two or three tyrosine kinase inhibitors. And you can still get some, 20%, 25% of patients to respond to this treatment option.

So now we have a wealth of drugs. We have five tyrosine kinase inhibitors, plus these other drugs, that gives us the options for good treatment for most of these patients.

Slide 29: Some Safety Notes
On the next slide I am showing you just as a precaution again, because patients are now living and taking treatment for a long, long time, just a few notes about some of the side effects that we need to keep an eye on.

About Gleevec, one thing that I have to mention, is that after more than 13 years of using Gleevec, we don't know that there are any bad things happening when patients take the drug for a long time. Of course, some patients have some side effects, diarrhea, muscle cramps, edema, etc., but we don't know that the long exposure is causing a greater risk of other things, other cancers or other things. So that is reassuring because, again, patients are taking these drugs for many, many years.

Sprycel, we've learned that there are some side effects that can happen in a few patients, like accumulation of fluid around the lungs, sometimes elevation of the blood pressure on the pulmonary arteries, not the blood pressure that you measure on your arm, but the one inside your lungs that can cause some shortness of breath. Now these things are not common, but it is important to again to always discuss any problems that you are having with your doctor, so that we can look into whether some of these rare side effects, but important, may be happening.

With Tasigna, the same thing, generally a very well tolerated drug. There are some issues with the heart that for the most part can be handled well if we keep an eye on the potassium and the magnesium. We know that some patients can have blockage of their arteries in their legs or in their hands, again, things that are not common, but that need to be discussed with the doctor.

DR. JORGE CORTES:
With Bosulif, diarrhea is the most common thing. It's very common with this drug, but it's usually something that can be managed and can go away after a couple of weeks or so.

With ponatinib we do see also some blockage of the arteries in the extremities, sometimes an inflammation of the pancreas.

With omacetaxine the counts drop significantly and need to be monitored.

And all of these drugs, one of the chronic things that we're trying to figure out a little bit better, fatigue. It's a common symptom. It happens with all of them. There are a lot of studies trying to understand why this happens and what we can do about it, so it is important to discuss with your doctor.

Slide 30: Take Home Message
So the last slide is a conclusion. I would just summarize to say we have great therapy for CML. I think with proper monitoring, with proper management, taking the medication without interruption or with minimum interruptions, discussing any problems with your doctor, managing these problems well, most patients would do well in the long term.

I need to emphasize clinical trials are still very important. We need to see how we can improve the patients getting into these complete molecular response, how we can get more of those patients there, can we stop treatment in a safe way in patients. There's a lot of studies, adding things to Gleevec to see if that can get us there. So all of these clinical trials are perhaps now even more important than ever, to make sure that we have the best outcome for our patients for many, many years to come.

So I'm going to stop here and I thank you all for your attention.

Slide 31: Question and Answer Session

MABEL MAIA:
Thank you so much, Dr. Cortes, for such a clear and informative presentation. It is now time for the question and answer portion of our program.

Our first question is from the web from the English audience. "I have been on dasatinib for almost eight years. Would it be a really bad decision for me to discontinue taking the medication? I have done well with very little side effects, but I feel like it is affecting my memory a lot. Have there been any studies on Gleevec and its implication on cognitive development?"

DR. JORGE CORTES:
Thank you for that question. And this is a very topical question. And again just to emphasize, the question is about can we discontinue treatment on somebody who's taking Sprycel for many years, seven years, and part of the interest of this question is some cognitive issues with the Sprycel.

The first part of the question, whether it's safe to stop therapy, it is not safe to stop therapy like we say here, cold turkey. You cannot just stop treatment and see what happens. I think that the way to address the question about stopping treatment is, first of all, we need to know what kind of response we have. On a patient that does not have a complete molecular response, sustained for two years, and that has been measured with a PCR that has at least 5-logs of sensitivity, and that means that you need to discuss

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with your doctor to make sure that all of these criteria are met, I don't think it is safe to stop therapy. We have had anecdotal experience of patients who for one reason or another stopped treatment when they don't have these criteria, and some of these patients have even gone to accelerated or blast state. So you don't want to put yourself at risk if the conditions are not met.

Even if the conditions that I mentioned are met, you need to have very close follow-up, very well organized. Usually we do molecular testing at least every month, to make sure that if it's going to come back, you can detect that very early. So this is something that needs to be discussed carefully, ideally in a clinical trial, or somebody who has a lot of experience with CML, to minimize the risks of having something that's now a good response converting to something that could be very serious.

Cognitive issues are important and, again, as we've moved from the bad diagnosis of leukemia, we're starting to go into these chronic issues. And we are indeed seeing that there are cognitive issues with these tyrosine kinase inhibitors. It happens a little bit with all of them. I don't think that we understand the mechanism well. But this is one of the things that should be addressed. We have a whole team, for example, here, that helps us evaluate this. Some of these things are minor and with some interventions that are maybe just sort of like exercise to the memory and things like that, can be addressed. Other times dose adjustments can help. Other times we use other medications to try to help with that. So there are different things that can be done about these side effects, but it is unquestionable that we do see perhaps more in a few patients, but we do see it in some with these drugs.

MABEL MAIA:
Great, thank you, Velora, for your question. Operator, we'll take a question from the telephone audience, please.

OPERATOR:
The next question comes from Amy in Ohio. Your line is now open.

AMY:
What is the percent of CML patients now that need to have a stem cell transplant?

DR. JORGE CORTES:
The question is what percentage of patients need to get a stem cell transplant and I am glad you asked this question because I didn't talk about stem cell transplant. And let's not forget that that's a very important treatment option that we've had for many, many years.

Fortunately, because of the excellent results of treatment with these new drugs, we have excellent results with minimal problems, particularly minimum mortality, and that has made transplants much, much less common in CML. However, there are patients who may not have responded well to two or three drugs and where transplant may need to be considered. I think that nowadays perhaps not more than 5% of the patients end up getting a stem cell transplant, but it is always something that has to be discussed with the doctor. At the time of diagnosis we don't really do it nowadays, but once, if the situation is not going well, if the response is not good, then you need to start discussing this with the doctor. We don't do them too frequently after just one TKI, but it is appropriate to at least start the conversation to understand the treatment options and the possibilities.

MABEL MAIA:
Thank you, Amy, for calling in. Our next question comes from the Spanish audience. It comes from Paulo. He wants to know, "Can you talk about fertility in male patients on dasatinib?"

DR. JORGE CORTES:
Gracias. So the question is on fertility for male patients on dasatinib. And I would extend these to on any of these tyrosine kinase inhibitors.

Well, first of all, we have to acknowledge that the information we have is still relatively limited. At the beginning when we were starting to use these drugs, the recommendation was for male patients to avoid having their spouses or their significant others pregnant, because of the lack of knowledge about what may happen to the baby.

With more time, we've come to believe that there seems to be not much of a risk for the baby from the father. So there's some small series and some anecdotes and all of that, where in general for male patients it doesn't seem to have a risk for the baby.

So today there is no absolute contraindication for a male patient who is taking dasatinib or any other drug, like these, to father a baby.

Of course, like in any pregnancy, you'll occasionally see minor things, but they seem to be the kind of things that we see on any pregnancy. So right now we just let the patients know that the information is relatively limited, but there's no formal contraindication.

MABEL MAIA:
Thank you, Paulo, for submitting your question. Our next question comes from the web from Robert. "I was on Gleevec for over three years and it stopped working. My doctor is going to put me on Iclusig and also try me on a stem cell program. What's your opinion?"

DR. JORGE CORTES:
So the question here is about a patient who's received imatinib for a long time, eventually it stops working and what is the opinion of doing Iclusig and/or a stem cell transplant.

One of the advantages of having these many treatment options is that you can select them based on the different characteristics of the disease and the patient and all these things. The best approach depends on what does stops working mean, what kind of response do we have at this point, what kind of side effects we have had with Gleevec, are there any other comorbidities that may make one drug, at least in principle, a better fit than the other drug.

So all of these questions are the things that we take into consideration to help an individual patient make a decision. So right now in a situation of a patient who's lost the response to Gleevec, for example, you have four or five treatment options that can be considered and as I mentioned to one of the earlier questions, even then, starting at least a discussion of a transplant is appropriate. So all of these options are appropriate, which one is best for an individual patient, needs a long discussion, evaluation of each one of the treatment options and good pros and cons discussion and make sure that you understand everything and go with whatever what may be the best approach. And understanding that many times there's more than one good approach for an individual patient.

MABEL MAIA:
Thank you, Robert, for your question. We'll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Veronica in Kentucky. Your line is now open.

VERONICA:
Yes, Doctor, you've already answered one of my questions. But my son has the CML that he developed just like last year. He's been on Tasigna about 16 months now and he says that he's already like in remission, where they've cut back on his medication. Now you answered the one question, my concern, his concern about like if he would start a family. So my other question that he worries about is because he's so young, he claims that it's mostly older people that actually develop the CML, and the long-term effect, like if he's on this for years, if you're never allowed to go off of it, whether you'll have more of a danger now of having organ problems, with other organs in the future.

DR. JORGE CORTES:
Thank you for that question. One of the questions was about a male patient, the ability to have a family, we talked about that. But the second question was about a young patient who is responding well, doing well with treatment with one of these drugs, Tasigna in this case, what's going to happen with many years of taking the drugs, if this is going to have to continue for the foreseeable future.

One thing I mentioned is that we have not seen that taking the drug for ten or 15 years really causes any damage to the body in any way. The great majority of patients, we don't have any evidence of any of this happening.

Now could it be that taking the drug for 25 or 30 years or 40 years, if you're talking about, let's say, a 20 year old, 40 years of taking the drug potentially is a possibility because living 60 years is well within the reach. We don't know, we don't know what can happen.

Now if we think about it, that's very true for many of the drugs that we use for other things. And if anybody is taking a cholesterol drug and thinks about the same thing, what happens if you take a cholesterol drug for 30 years, we don't know. We haven't had them for 30 years. So many times the medications or even the supplements that we take for some time, we don't know what happens for a long time. But we don't have any evidence that it'll cause anything bad.

One of the concerns at the beginning was whether we would be seeing more cancers in patients who took these drugs. And we certainly have seen some cancers in some patients who had CML and now responding well, but taking these medications, they develop other cancers. But what we've been able to understand by now is that they don't get other cancers more frequently than anybody else. So certainly a patient can develop a colon cancer, a lung cancer, a prostate cancer, whatever, but it's not more frequently than anybody else who does not have leukemia, who does not have to take these medications.

So we do not know that there is a long-term adverse effect of taking these drugs for 20, 30 or 40 years, but we don't have that data because these drugs have only been available for about 13, 14 years.

MABEL MAIA:
Thank you, Veronica, for calling in with your question. Dr. Cortes, our next one comes from the Spanish audience from Manuel. "Can you participate in a clinical trial if your disease is undetectable? There is a study that will be forthcoming in Boston to see if patients can get off Gleevec. I believe the doctor will be using as asthma medication as part of the trial."

DR. JORGE CORTES:
Gracias, Manuel. The question is can you go into a clinical trial if you've been completely undetectable and specifically they mention about a study about treatment discontinuation. And the answer is absolutely yes. There are a lot of trials that we are doing in many parts of the country and the world, looking precisely at, for example, the treatment discontinuation. And that is the way to do it. If you are interested in considering a treatment discontinuation, the optimal way is to go into a clinical trial because that's going to have a very, very close monitoring, so that if the disease is to come back, we catch it early, we prevent it from going into the more advanced stages, and maybe you have to go back to the treatment and the treatment discontinuation didn't work in terms of being off the drug, but at least you don't put yourself in harm and getting into more problems.

So there are studies, anywhere from at the time of diagnosis, many studies looking at even better ways of doing the treatment from the beginning, patients who are having a little bit of side effects with one drug or another, maybe changing to another, patients who are completely intolerant or resistant to one drug, patients that have good response, but not completely negative, can we make them negative, all sorts of clinical trials and all of these are good options, depending on what the specific situation.

MABEL MAIA:
Thank you, Manuel, for submitting your question. Our next question comes from the web, from the English audience. "What kinds of options are to monitor CML if the PCR tests are not available?"

DR. JORGE CORTES:
Thank you. So the question is what can you do to monitor the CML if the PCR is not available. And here we need to figure out first if it's not available because the hospital where I'm going doesn't do it, well, there are many ways of doing the PCR in other hospitals, to send it to other places. I'm sure that there's some patients of mine in the audience, I've already heard one, and they know that they get the blood drawn at home and they ship it to us, so we get the blood, the PCR done from a distance at the laboratory here, but they ship it to me. So maybe that's something that can be considered.

Now in some instances it just doesn't happen. Let's say a patient who lives in a country where PCR is not available, etc., well, then you can do the cytogenetic analysis, you can do the FISH. Those two are tests that can help you assess the response and because you want to know that at least the patient has a good chromosome response, if you can do one of those, at least you know you are in what's the minimum that you can accept. And usually you can find at least one of those tests available in some place. Of course, sometimes the cost is an issue, but there are assistance programs that can help try to get access to these tests if the problem is the cost.

Slide 32: LLS Resources

MABEL MAIA:
Thank you, Forest, for submitting your question. And actually thank you all for your questions today. Our program has come to a close. We hope this information will assist you and your family in your next steps.

If we were not able to get to your question, please call the LLS Information Specialists toll-free at 1-800-955-4572. Or you can also reach us by email at infocenter@lls.org. Our specialists can provide you with information about CML research and clinical trials and other questions you may have about treatment and financial assistance.

Slide 33: LLS Resources
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 living with CML and their families in any region of the world who need support services. You can contact The Max Foundation at www.themaxfoundation.org.

Please help me thank Dr. Cortes. We are so grateful he has donated his time to us today. On behalf of The Leukemia & Lymphoma Society, Abrale, Alianza Latina, Dr. Cortes and I would like to thank you for sharing this time with us. Good-bye and we wish you well.

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