

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Welcome and Introduction

Carson Jacobi, MPH

Hello everyone. My name is Carson Jacobi, MPH, and I am the Vice President of National Education Programs for *The Leukemia & Lymphoma Society*. On behalf of the *The Leukemia & Lymphoma Society*, we welcome you to today's program titled ***Current Treatment Options for CML: Progress in Research*** featuring Drs. Michael Mauro and Neil Shah. We thank them for their time today, and we would also like to acknowledge and thank Novartis Oncology for their support of today's program.

We have more than 1000 individuals registered for our teleconference/Web program today, and most of our participants are within the United States, but we do have several participants from other countries, and they are: Australia, Brazil, Canada, Denmark, Egypt, India, Jordan, New Zealand, Oman, The Philippines, Puerto Rico, Singapore, South Africa, Thailand, the United Kingdom and Venezuela. A special welcome to all of you.

Today's program is being audiotaped and transcribed for future posting on *The Leukemia & Lymphoma Society's* Web site. In late January, we will post the presenter slides, the audio files and the transcript for you to download.

As I mentioned, this is a teleconference/Web program, which means that we have people participating by telephone and following along with the slides in their packet, and we have Web participants who are listening and watching the presenter slides live.

For those listening by telephone, your program materials were sent via US mail; and for some who registered recently, your packets will arrive shortly. Your program packet includes the agenda for today's call, the presenter slides and highlights of *The Leukemia & Lymphoma Society's* programs, including a packet to order additional publications and catalogs. You'll also find a blue program evaluation form, and we encourage you to look through those materials at your leisure if you have not already done so.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

And for nurses and social workers, this is a continuing education (CE) program, and you will need to complete the CE evaluation form, to claim your 1.5 credits hours.

After our keynote presentations, we will open up the program for questions to our expert panel. And, as you listen to the presentations, think of any questions that you may have.

So, because we do have hundreds of people participating in this program today, speakers may not be able to get to all of your questions. However, you can call the *The Leukemia & Lymphoma Society's* Information Resource Center and speak with a master's level oncology specialist who can answer your questions or help you obtain more information. And the Information Resource Center can be reached by calling toll-free 1-800-955-4572, Monday through Friday, 9:00 AM to 6:00 PM Eastern Time.

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

John Walter

Thank you, Carson. I would like to add my welcome to all the patients and caregivers and healthcare professionals on the call today.

We are fortunate to have as our presenters, Dr. Michael Mauro and Dr. Neil Shah, both world-renowned CML specialists. We appreciate their dedication to supporting the mission of *The Leukemia & Lymphoma Society* through their research and clinical practice. I wish to thank them for taking the time out of their busy schedule to provide us today with current treatment options for CML.

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

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

illness with good quality of life.

Since its founding in 1949, the LLS has invested more than \$680 million for research, specifically targeting blood cancers. We will continue to invest in research for cures and programs and services that improve the quality of life for patients and families. This teleconference is one step on the road of your journey to managing your life with CML.

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

Carson Jacobi, MPH

Thanks so much, John. I now have the pleasure of introducing Dr. Michael Mauro, who will provide an overview on treatment options for newly diagnosed patients. Dr. Mauro is an associate professor for the Center of Hematologic Malignancies at the Knight Cancer Institute at Oregon Health & Science University in Portland, OR.

Dr. Mauro's clinical focus is CML as well as other myeloproliferative disorders, and he is currently directing clinical trials for patients with CML in all phases. And his research interest is the monitoring and managing of minimal residual disease, optimizing response to therapy in CML and assisting with decision-making for patients considering stem cell transplantation and nontransplant therapy.

We're so privileged to have him with us. Please join me in welcoming Dr. Mauro.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Treatment Options for Newly Diagnosed Patients

Michael J. Mauro, MD

Well, thank you, Carson. Thank you to you all. Good morning, good afternoon, good evening, depending on where you are.

What we're here to talk about this morning is current treatment options for CML. And if you didn't know it, we've just recently been to what's called our American Society of Hematology (ASH) Annual Meeting, where we see new research and new advances in all of the blood cancers presented and shared among healthcare providers. And we have some information we can share about that and we'll, hopefully, give you a good overview of the state-of-the-art in CML.

So let's just, by way of background, talk about CML a bit. I start with this because really the route of CML has a lot to do with treatment and the focus of our treatment efforts over the last decade.

CML is really caused by an error in the blueprints of the DNA of our blood progenitor cells or stem cells.

An important question I'm often asked is, "Is CML inherited?" And, as far as we know now, we do not believe that to be the case.

As well, people diagnosed, or those loved ones of people diagnosed, wonder how did it happen? Was there some risk for exposure? And we really, as well, only have very clear-cut, rare risks that might cause CML, such as high-dose radiation or nuclear accidents and the like. Otherwise, it really is thought to be probably a common mistake that happens in the blood as it's dividing and leads to a disease in a smaller number of individuals.

What makes CML unique is that it's one of the few cancers with a discrete singular driver or switch that's thrown that causes the disease. And, as you know, or may not know, the Philadelphia chromosome really

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

lies at the heart of CML. The Philadelphia chromosome is really an abnormal chromosome. It's the short chromosome #22 over on the right side of this slide with a BCR-ABL fusion.

So what happens, and I often refer to this as, "chocolate in my peanut butter and peanut butter in my chocolate." We have 2 chromosomes dividing and inadvertently swapping the genetic material and 2 pieces of gene material or blueprints are juxtaposed that shouldn't be there; that's called a translocation, and the 2 bits are called BCR and ABL, and when they're fused together they create blueprints for an abnormal switch to be presented in leukemia cells, which prevents them from shutting down or responding to their normal cues as they should.

So how do we profile someone with CML (ie, profile the disease at diagnosis)? First, we want to make sure that what the blood disorder is really does carry the Philadelphia chromosome, and we need to identify that. Second, we want to know what stage the disease is in. Is it in a chronic stage or chronic phase, as most persons who present with CML are? Or has it shown more instability and moved on to a more advanced stage? And these are important decisions points regarding treatment.

The Sokal score is a score that physicians and healthcare providers can apply. It's basically taking the presenting features of someone with CML at diagnosis from their blood tests; the number of blast cells, their platelet count, their age, the size of their spleen and some other cell counts as well can be added in to make the score more complex. But this really helps us, again, profile the CML and to know a bit about how it might behave, how it might respond to treatment and what we might expect.

So, looking at response in CML, once we begin treatment, we are looking at a fairly large volume of CML at the time of diagnosis. When someone sees their doctor and is diagnosed with CML, the blood counts are often very elevated and the marrow contains a fair burden of CML, and I call this an inverted iceberg. And the response levels that we're looking for in CML are represented here.

As we skim off the top, we see that the blood counts normalize, the spleen will shrink, and this is what's called a CHR, or a complete hematologic remission. This is the first step in improvement in someone with CML.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Below that, the next step is measured by bone marrow testing, and this is where we see levels of the leukemia cells that bear the Philadelphia chromosome in the marrow reducing, and it's a fairly simple equation. As the majority of the cells are now normal and only a minority, up to 35% are positive, we call a major cytogenetic response, an MCYR. Intuitively, when the level is down to zero, we call it a complete cytogenetic response. But as, hopefully, I've demonstrated in this diagram, we still have a fair bit of disease burden to go.

We can measure further improvements by looking at molecular response. When the disease burden shrinks down a bit more, we can identify what's called a major molecular response, or an MMR, and that's a relevant endpoint as well, although cytogenetic response is an overwhelmingly important landmark to reach. We can see patients get down to very low levels of CML detected by a test called polymerase chain reaction (PCR). And, indeed, there are some patients who are below the level of detection of PCR. Their doctors have told them, and I've had the pleasure of telling patients, that we cannot detect the leukemia any longer. This is called a CMR, or complete molecular remission.

I want to caution you to understand that that definition doesn't mean that there's absolutely no leukemia, unfortunately, because it could; we just simply can't measure below a very deep level of remission. And, obviously, as time goes on, we'll hopefully be able to clarify and further advance knowledge around that status because it's becoming more and more common.

If we think about response after diagnosis of CML, CML treatment, I like to refer to it as the treatment and the response that we're looking for, it really is a marathon. It's not a sprint to get to the finish.

Right now, in 2009–2010, we're speaking still about maintenance therapy, ongoing therapy. After therapy is initiated, our landmarks or response occur over time and we're looking for expected improvements to consider the treatment successful. So we have landmarks that we want our patients to hit and we guide our decision making accordingly.

If you look at that iceberg again, just to put it into context. After about 3 months of treatment, we expect patients should have their blood counts no longer elevated, their spleen no longer enlarged and have had a

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

complete hematologic remission. And this is based on some of the latest guidelines published by CML physicians globally.

If we think about what we might expect at a later timepoint, at 6 months, now we would like to see the bone marrow response be a major response at a minimum, really, to be considered ahead of the game or on target for treatment. Some cytogenetic response is considered adequate but, really, a major response is what we're looking for. As we move ahead in time to 12 months or 1 year, we want to see a complete cytogenetic remission. Moving further, 18 months or so, now we're looking for CML to only be detected in PCR testing, and we like to see patients to be considered an optimal response, have had a major molecular response. So you can see it takes some time and, again, getting down to those lower levels, fortunately, happens for the majority of patients and we have various different landmarks to hit.

So what's considered a good response, again? A blood count elevation and spleen enlargement, those need to be resolved by 3 months. A complete cytogenetic response we're looking for by 12 months, at the latest 18 months.

What does this mean? If someone is able to achieve a blood and a cytogenetic remission within those time frames, their risk of losing response is markedly low: 2% risk of disease relapse per year that declines to a very low level, less than 1% per year after 4 years.

What that means is that, in the first 2 years there might be a small risk, but after that, there's even a smaller risk. And many of us in the field and, of course, those afflicted with CML, might have thought the opposite, that their risk might have increased over time, and that doesn't seem to be the case.

Faster cytogenetic responses or bone marrow responses, as I've hopefully demonstrated for you, would be considered optimal. If we can see the majority of cells are normal by 6 months, or even a complete bone marrow remission by 6 to 12 months, that's really a predictor of increased chances of being quite well protected over time against relapse or progression. So, of course, we can measure the best, but we really want to define what is really required to be in good remission for CML?

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

We focus a lot on PCR testing. As the healthcare team, and of course as patients, we want to advise you about your minimal residual CML levels. And the bulk of our monitoring is done by PCR at this point, which is great news because it means most patients are in a very deep remission.

A PCR test can detect 1 leukemia cell in a thousand or even really up to a million normal cells, and our better tests, which are more commonly available, are at a level of 1 in 10,000 to 1 in 100,000, or up to 1 in a million. They can be qualitative, say yes or no, the leukemia's present or absent. Those aren't as helpful for us, although they have some role, but we really prefer quantitative tests, which tell us how many cells we can estimate are present. What's the burden of CML remaining, so we can track progress over time, track stability and, hopefully, have confidence in our ongoing response.

If we look at PCR monitoring, the quantitative method, again, is preferred. Some problems exist though. Different labs have different results and standardization amongst different laboratories. The patients may go to their doctor and have their studies done at one laboratory, and then if they move or if the physician uses another laboratory, the language isn't, unfortunately, common right now. Until then, we recommend that patients try to stay with one lab, one provider using one lab, if they can, because that really helps us track their progress. Again, negative results where there was complete remission really depend on the quality of the sample and the quality of the lab.

So, not that it's not an excellent place to be, but a complete response or a PCR negative status, that doesn't mean that the CML may be completely gone. It certainly doesn't mean the treatment can be stopped, although we're doing some research in that area, and we just aren't ready yet. And we haven't decided on fixed points or agreed levels per se with regards to those very small residual thresholds that, hopefully, an increasing number of patients will cross.

So what is a good molecular response or PCR response? A 3-log reduction in the PCR level, and this is from the start of treatment at any time but, ideally, after 12 to 18 months represents what we call a safe haven or a safe harbor. And if patients are in that safe haven or harbor, their risk of relapse optimize and really represents less than 1% that declines to even lower levels over time.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

What is a 3-log reduction, just to remind us. It means that the leukemia signal is 10 times smaller than when a complete bone marrow remission occurred and the leukemia is 1/1000 of the size it was when we started.

That being said, and those are optimal types of responses, a stable cytogenetic response occurs first and is quite important, and that represents a 2-log reduction; just to help you with some of the terminology.

As people move through treatment, they're often wondering, "How am I doing? When should I consider a change in therapy? Are there warning signs, rather than in the setting strictly in relapse or side effects that are intolerable?" As physicians and as patients, as well, it's our job to sort of keep our eye on the ball, and if a patient hasn't had a blood response after 3 months of this current front-line therapy of imatinib, that's a reason to change.

If the patient hasn't had any reduction in the Philadelphia chromosome level in their bone marrow after 6 months, that's also a reason to change.

If the patient is greater than 35% after 1 year, this also represents a reason to change. These are clear-cut recommendations from guidelines published from global CML experts that convene and review the available data.

Let's talk a little bit about some of the research and some of the questions we are addressing in the field. What about higher doses of imatinib. Are they better than standard doses? We've been studying this question for many years and randomized studies haven't shown as strong a difference as we might have expected. There definitely is a trend to faster response in the patients who could maintain the higher doses of therapy. If patients needed to cut the dose down or take breaks due to side effects, that often diminished the benefit they were able to achieve.

As well, we have the ability to measure levels of imatinib in patients, and drug levels actually may help predict the likelihood of achieving response. So while we can raise the dose as an experimental option, we have a tool available to us to help us identify whether patients are on the right amount of drug and the level

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

in their system is adequate. More toxicity and more side effects do occur with higher doses, so we still haven't closed the book on this question yet.

Regarding the question of drug level monitoring, it definitely is worth checking if someone has less than an optimal response or if we're concerned their exposure might be less or if they have unexpected toxicity. It also may be worth adjusting in a newly diagnosed patient, but we haven't all the data yet. Some day we envision that we might want to test patients early to fine tune their therapy, to individualize it, personalize, if you will, to make sure that their CML is sensitive, their drug levels are adequate and so on. And that's really the future, hopefully, of CML.

One of the most exciting presentations at this year's ASH meeting revolved around what we might do for newly diagnosed patients in the future with CML. As you might imagine, 2 drugs approved for patients with imatinib intolerance or resistance, nilotinib and dasatinib, both being aggressively studied for patients with newly diagnosed CML. Should we be using newer drugs rather than our standard imatinib at diagnosis? And the early data suggested that higher response rates and also faster responses were achievable with newer therapy.

This is similar to the early data I alluded to when we used higher doses of imatinib, but the randomized studies that were presented showed that, not only was the use of second-line inhibitors potentially more favorable with regard to response, they might lower the risk of progression, they might have quite a good side effect profile. The future is quite bright in this area and I expect some exciting news potentially in 2010 regarding both of these agents (ie, more data from trials and, potentially, even an FDA approval for newly diagnosed patients with the option to use one of our newer drugs that we've developed).

As patients, the bulk of patients currently, in 2009 and 2010 who are, hopefully, in a safe remission, wonder about the long-term prospects, and they actually start to ask the question, "Will I ever be able to stop treatment or is this needing to be a maintenance treatment?" We, too, ask the same question, and I want to emphasize that this is really still a research question.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

We have started to probe into this area with small studies with short follow-ups that average less than 2 years. But what we've seen is some patients, although it's 50% or less, have not shown evidence of their CML returning, their PCR turning positive, when they had a very swift and very definitive response to imatinib and had no detectable CML for an extended period of time and then discontinued therapy. These patients, they're small numbers being very carefully followed in clinical trials. And, again, I would not recommend this at this point, but why?

Our concern over the quality of a remission that you would regain if you lost it after stopping, we're uncertain about that. We'd also like to understand how to predict which patients may or may not have different disease characteristics and potentially could or may not be able to stop.

As well, we're looking at newer drugs and other strategies such as things related to the immune system, vaccines and what not, that might help us finish the really tremendous job done with imatinib, or maybe be able to do better with newer drugs, putting patients in deep remission.

There is still a question always out there regarding when stem cell transplant is needed. This is clearly still a curative option in CML and remains so. When CML is in an advanced stage and long-term remission is less likely, stem cell transplant really should be considered as a very reasonable route to optimizing long-term prospects.

If someone has chronic phase CML, that's quite brittle, and they have little or no response to treatment, either before or, certainly, after switching to newer treatment, that would be, again, a time to reconsider stem cell transplant.

And there are certain types of resistance that us, as CML physicians, and patients may know about, specific mutations in the BCR-ABL targets. Specifically, something called a T315I mutation. This is a specific kind of resistance in CML that isn't right now treatable by approved drugs, although I should say that there are some exciting drugs in development that might be able to address this, but right now that is a difficult situation and may be a time to reconsider stem cell transplant.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

I'd like to wrap-up with some conclusions. Imatinib at 400 mg is still the standard therapy for patients with CML. We do have some exciting news from randomized studies comparing imatinib to nilotinib or dasatinib, and stay tuned for any changes. We might see further progress in CML in the next year.

We need to identify which patients are least likely to respond or who are at highest risk for relapse. Again, we'd like to really personalize or optimize therapy for all patients.

Some of our tools are fairly developed, like drug level monitoring, although we need to further research this question to incorporate it into our armamentarium. And, certainly, achieving landmarks of response are predictive of long-term outcome and we need to work as healthcare teams and patients to stay on target.

At the diagnosis of CML, treatment options are very powerful. As I tell my patients, CML really tells us what is necessary to do as we treat, if we know what to look for. So we don't have to make all the decisions at the first moment. We need to follow carefully, know what we're looking for, and if we don't get there, be proactive rather than reactive.

Patients and doctors need to navigate together to optimize success and our further research is really going to provide us with more tools for monitoring and, also, novel treatment options.

I thank you for your attention.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Emerging Therapies for Relapsed/Refractory Patients

Carson Jacobi, MPH

Thank you so much, Dr. Mauro.

It is now my pleasure to introduce Dr. Neil Shah, who will review emerging therapies for relapsed/refractory patients.

Dr. Shah is an assistant professor in the Division of Hematology and Oncology for the Department of Medicine at the University of California, San Francisco School of Medicine in San Francisco, CA.

Dr. Shah's initial postdoctoral research focused on understanding why imatinib stops working for a subset of CML patients. He published the first preclinical studies of dasatinib and was involved in its clinical development for the treatment of imatinib-resistant and imatinib-intolerant CML. He's currently working to further improve the success of targeted therapy for CML and to expand his treatment paradigm to other blood-related cancers.

Please join me in welcoming Dr. Shah.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Neil P. Shah, MD, PhD

Thanks, Carson, and thanks to Dr. Mauro for an excellent introduction.

What I would like to do is talk about imatinib in a little bit of a different light. Now, first and foremost, I want to say that, without question, this was a revolutionary therapy that's changed the way that a lot of us approach how we think about treating cancers and how we should think about it. And it's allowed us to ask questions and set an increasingly higher bar in terms of what we're trying to achieve in patients.

And I've been participating in this event over the past several years and, you know, as time goes on, we certainly, as I mentioned, have the luxury of asking, "Well, how well is imatinib doing, and can we do better?" And, as time goes on, you know, it clearly seems that there are patients, and we can recognize this more and more, who can perhaps benefit from other forms of therapy. And we also, as time goes on, can see more and more of the shortcomings of the particular drug, and the mode of therapy.

I guess, you know, you can almost liken this to when you first fall in love with somebody and then you maybe get married and everything is great, and over time, you can start to see some of the shortcomings a little bit. So, I want to phrase this a little bit as sort of a half-full, half-empty issue.

Now I think, as Dr. Mauro mentioned, imatinib, at a dose of 400 mg once daily, is generally well tolerated and, certainly, at this point in time, should be considered first-line therapy for chronic phase CML patients. Now patients with the more advanced phases of the disease, should be started on higher doses of imatinib, but chronic phase patients, 400 mg remains the recommended first-line therapy.

And, as Dr. Mauro alluded to, the majority of imatinib-treated patients, if they are started in the chronic phase, do achieve very deep responses, deep cytogenetic, complete cytogenetic responses, and quite frequently major molecular responses. And once patients get to this level of response, most frequently they are durable. Not always, and I think what we're learning is the deeper the response over time, generally, the better patients will do.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

And, as Dr. Mauro alluded to, patients who do respond deeply, appear to have a low risk of relapse as time goes on, and we do understand from large cohorts of CML patients who were treated with imatinib, that the majority of patients who have loss of response events on imatinib therapy, the majority of these events occur within the first 3 years. And this, I think, speaks to the importance of careful monitoring, especially during this time period, and we can talk a little bit more about that, and Dr. Mauro did mention that as well.

One other thing to note is that more patients are becoming PCR undetectable or having this complete molecular response achieved with the passage of time on imatinib therapy. And so, I think there's certainly reason to believe that people who are tolerating imatinib and responding well, that the quality of those remissions may actually improve over time and without question, and I think this is something we all need to remember, imatinib clearly has made a major impact on the survival outlook in chronic phase CML patients.

Now, bear in mind, it has not even been 10 years since this drug has been approved, and so it's difficult to really understand the full nature of the expense to which survival may be impacted. But, clearly, with only a few years of follow-up, it's doing remarkably well and, certainly, far superior to any prior treatment, medical treatment modality that we had.

Now, if we take the flip side and really look at some of the shortcomings of imatinib, I think we have to bear in mind that there is a substantial proportion of patients who do develop resistance to imatinib. There are patients who do not respond adequately initially, but for these patients, and also for patients who are highly intolerant of imatinib. And, again, this is generally a very small proportion of patients that have a high degree of intolerance to imatinib. But for these patients, it is clear that they could benefit from other therapies. And, of course, not everybody has the opportunity or not everybody would be an excellent candidate for a bone marrow transplant. And given the side effects of that therapy, it's something, if possible, we would like to avoid if we do have effective medical therapies.

As Dr. Mauro alluded to, imatinib does not appear to be curative at the present time, although there are patients who are undetectable by PCR. Of course, we cannot say with any confidence that being undetectable can be equated with being cured. Now there may be a proportion of patients who are undetectable, who are, in fact, cured. But, of course, it's going to take years if not decades to really

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

determine this, and it's going to take follow-up of patients who've been on clinical trials and discontinued their imatinib before we know the answer to this.

And, of course, those of us who do remember what this disease was like just 10 years ago, we do exercise a bit of caution with respect to this issue of discontinuing imatinib. Because, although there have been some studies looking at several dozens of patients, as Dr. Mauro alluded to, who have had a complete molecular response on imatinib and then gone off therapy, and after 2 or 3 years, a good proportion of these remain in complete molecular remission. I think, in my opinion, it would only take 1 or 2 patients who would develop a sudden transformation of their disease, while they were interrupting imatinib therapy. Should 1 or 2 patients develop a sudden transformation of their disease to accelerated or blastic phase, then I think enthusiasm for this approach would significantly dampen amongst CML experts.

I completely understand the desire of patients to want to discontinue therapy at some point. I want to be clear that it remains, I think, one of the most important goals moving forward in the future. But, at the present time, there's a lot of discomfort for that reason amongst CML experts to recommend discontinuation in patients who are responding very deeply and tolerating the medication well.

And to put into perspective the proportion of patients who could benefit from other forms of therapy, we estimate that about a quarter of patients, within the first 18 months after initiating therapy, could, in fact, benefit from some other form of therapy; such as the approved second-line agents that Dr. Mauro referred to dasatinib and nilotinib.

Now one thing to note is that with imatinib, again, getting to this glass half-empty issue, is that clearly the best responses that are achieved with imatinib are achieved in those patients in whom the drug is reasonably promptly started following diagnosis of chronic phase disease. And what this slide is basically showing is the likelihood of developing a loss of response to imatinib 3 to 4 years after initiation of therapy. And what I just want to point out is that the earlier within the disease course imatinib is introduced, the better patients will do.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Now you can see that for the accelerated and blastic phase patients, unfortunately, almost all those patients who start imatinib in that phase, unfortunately, their disease becomes resistant relatively quickly. But even if we look at what we call the late chronic phase patients, these were actually the first patients to take imatinib in any substantial number. And these were patients that had previously been treated with interferon, so this was going back to the late 90s early or around the year 2000 when imatinib had not yet been approved. So when imatinib was first approved, of course, the patients for whom it was immediately available, the majority of those had already had the disease for some time. And I just want to point out that those patients have a higher likelihood of losing response. And so prompt initiation of effective medical therapy, perhaps not surprisingly, is associated with the best outcomes, and you can see that as early as 3 to 4 years after initiation of imatinib.

Now there are some reasons why patients may not adequately respond to imatinib and Dr. Mauro went through very nicely the milestones that we want patients to achieve; be they measured at the hematologic level initially and then later the cytogenetic level by bone marrow, biopsy and aspiration and then also the molecular level by the quantitative PCR. There's, I think, a pretty reasonable body of evidence to suggest that some patients who do not respond adequately to imatinib, that for some patients the issue is really how well the target of the disease, which is BCR-ABL is being hit by the drug. And imatinib at a dose of 400 mg we know is not the most potent dose of BCR-ABL inhibitor but, clearly, for the majority of patients, it's more than adequate as you've heard.

But there are some patients, for one reason or another, for whom 400 mg is not adequate and some studies have, I think, pointed rather nicely to the fact that the problem may lie with the amount of BCR-ABL inhibition that is actually being achieved within the leukemic cells. And there have been some possible mechanisms postulated, and those are listed here. One has to do with plasma levels, as Dr. Mauro mentioned. There have been some studies suggesting that those patients that have lower plasma levels of imatinib, after a month of taking imatinib, have a lower likelihood of achieving the deep sort of response we'd like to see.

There have also been some studies that have looked at what we call drug pumps and these are proteins that pump imatinib into or out of cells, and varying levels of expression from one person to another may be

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

responsible for why imatinib, in some people, may not be associated with the same level of response at a dose of 400 mg as others.

This, of course, leads to the obvious question, “Well, what if we had a more potent agent than imatinib? What about higher doses of imatinib?” And then, of course, the second-line agents that we have a lot of confidence in as being more potent will, in fact this issue of patients not really responding adequately for the most part go by the way side? I believe that the initial response rates will be improved. Of course, there are clinical trials addressing this and, as Dr. Mauro alluded to, we heard about one of these, nilotinib compared with imatinib where, in fact, it did look, I think rather convincingly, that the proportion of patients who achieve this deep level of complete cytogenetic response by 12 months was superior to those patients on 400 mg of imatinib.

Now, I also want to say that it is likely to be the case that there will be some patients who, unfortunately, no matter how potent our BCR-ABL inhibitor is, will not achieve a cytogenetic response. And what we need for a cytogenetic response to occur is basically we need 2 things to happen. The first is, of course, we need the BCR-ABL expressing cells to disappear, and we think we should be able to achieve that, as I mentioned, with the more potent agents; but we also need a bone marrow environment that has enough normal remaining bone marrow stem cells that can repopulate not only the bone marrow but make all of the mature elements that we find in the blood. And without that, it can be very, very difficult, of course, to get a cytogenetic response because a cytogenetic response is defined as chromosomally normal cells appearing in the blood or in the bone marrow.

And so, there are going to be some patients who I think will probably be diagnosed, perhaps relatively late, after the disease had established itself. Now it's, of course, difficult to know exactly when the disease establishes itself, but I think that there will always be only a small proportion of patients in whom the likelihood of achieving a complete cytogenetic response may be low for this particular reason.

Now, in addition to patients not adequately responding initially to imatinib, we know there are patients who lose their response and there's some interrelationship between this. One of the reasons we really worry about people not meeting treatment milestones is because they are at higher risk for the development of

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

loss of response to imatinib. And we know a lot about the mechanisms that drive loss of response to imatinib, and listed here are the most commonly detected mechanisms. One is through what we call kinase domain mutations in BCR-ABL, and these are subtle changes where the drug binds to the BCR-ABL protein that at the time of resistance, BCR-ABL is subtly altered in such a manner that imatinib can no longer effectively bind; and we know this to be the most common cause of loss of response to imatinib.

There are some patients that have too much BCR-ABL at the time that they develop resistance so here we think of the problem as simply being the amount of imatinib that can really get inside of the leukemic cell is not enough to deal with a higher amount of BCR-ABL. And, again, of course, one of the things that's exciting about the second-line agents is that we know that not only in the laboratory but in the clinic, they are highly effective against almost all imatinib resistance-conferring mutations; and, in addition, they are more potent than imatinib. So, their promise in patients not only with imatinib resistance, but also in patients who are newly diagnosed is, I think, rather substantial. But, again, we do need to see the clinical trial data comparing these agents with imatinib more fully before making decisions as to whether or not to start patients on these newer agents.

Now, dasatinib and nilotinib, as Dr. Mauro has mentioned, are actually approved in the United States by the FDA and throughout much of the world as what we call second generation BCR-ABL kinase inhibitors. We know clinically they're effective in patients with imatinib-resistance or imatinib-intolerance. Dasatinib is approved for all phases of CML and for BCR-ABL associated acute lymphoblastic leukemia or also known as Ph-positive ALL. Nilotinib is approved for chronic and accelerated phases of CML.

What we've learned with these agents is although in the more advanced phase of the disease they are active, the responses are, unfortunately, not very durable. So, we come back to the issue that potent or effective therapies, rather, the therapies that tend to be effective, tend to do their greatest good the earlier within the disease phase that they are offered to patients. And I think these drugs will really be no different than imatinib or interferon in that regard.

Now these 2 new agents are generally well tolerated. There are, of course, patients with any drug who are going to be intolerant. One bit of good news is that there's very, very little cross-intolerance; meaning

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

patients who have to stop imatinib because of a bad side effect are highly, highly unlikely to develop that same side effect if it's what we call a nonhematologic side effect; meaning it's not related to the blood count on the newer agents. And that, of course, is good news because our hope is with more therapies, there will be agents that everybody will be able to have available to them that are, at least for them, not only effective but reasonably well, hopefully, very well tolerated.

Now loss of response to these drugs has, of course, been observed. We know that this is typically due to one of a small number of mutations for both of these and those are listed at the bottom. And actually listed at the bottom are the mutations that follow imatinib resistance that pose specific problems for one or the other of these agents. And so we're getting to the point of personalizing our approach in patients that lose response to imatinib whereby we can choose which agent to preferentially select in the second-line setting — so either dasatinib or nilotinib — based upon whether a patient has one of these potentially problematic mutations.

And I just want to say that while we would love to be able to be curing patients, at the present time there's really no compelling evidence that the second-line agents are doing any better than imatinib in this regard, but, remember, they haven't been around for as long as imatinib and I think this is something that we'll be interested in investigating as time goes on.

So, just to summarize where we are with these second-line agents, as I mentioned, these 2 are FDA approved. There are some investigational agents. The things that these agents all have in common is that, although they are more potent than imatinib in laboratory studies and although they are effective against nearly all imatinib-resistant mutations, there's one particular imatinib-resistant mutation, T315I, that is unfortunately, highly resistant to all of these drugs. And so when patients develop this particular mutation, we don't at the present time have an approved medical therapy for such patients, but I think there is some potentially good news which I'll mention here. And that is that there are investigational third-generation inhibitors. Some of these, the first 2, data were not really presented in a large amount in this particular study. The first drug there was some new data presented on and this can achieve some deep chromosomal responses in patients with the T315I mutation, as can XL228. Both those drugs are intravenous and have to

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

be given in a fashion that's perhaps not as convenient to patients. And, in addition, it should be mentioned that we think that these drugs can also suppress the blood count in anybody whether or not they have CML.

The agent that I have highlighted here, AP24534, is one that I find particularly exciting. This is a pill, it's a BCR-ABL inhibitor, that we don't think of as being very suppressive of blood counts, and there were some nice chromosomal responses observed, certainly, in chronic phase patients that have the T315I mutation. It's still very early in its clinical development, but I think this is, in my opinion at this point, the most exciting agent to come about in CML since the second-line agents, since dasatinib and nilotinib first made their splash.

Now, as far as where we are going in the future, as Dr. Mauro has said, I think an open question is, "How should we be treating newly diagnosed patients? Is imatinib the best way to go? Should we give imatinib only to select patients? Should we consider the second-line agents for newly diagnosed patients?" I think over the next year or so we'll get information from the randomized study of dasatinib versus imatinib. I think it's highly likely that both dasatinib and nilotinib will show the ability to achieve deep responses relatively quickly compared with 400 mg of imatinib. There are, of course, important safety issues that need to be answered before we could consider moving these agents to the front-line setting for all patients, but I think that that day will probably come before too long.

And other issues have to do with combining kinase inhibitors and, as I mention here at the bottom of the slide, it's important, of course, to incorporate mutation detection here in 2009 in patients who have loss of response or resistance to imatinib to identify the root cause of that and to choose the second-line agent appropriately.

And then my last slide here is that I believe that having more medical treatment options will probably further delay bone marrow transplantation. I think we do need to keep in the back of our mind that this is a potentially curative option that we do have available to a substantial proportion of patients, and, of course, we have a lot more long-term follow-up data with transplantation than we do with the medical therapies.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Again, I think that the T315I issue may become something for which we have medical treatment options. And then there are some strategies being crafted to actually see, can we take patients who have some low level of disease on imatinib or on dasatinib or nilotinib, and can we actually truly cure these patients? Can we not only convert patients to being molecularly undetectable, but down the road can we then back off on therapy and actually cure people? And, again, it's probably going to take years before we have the answers to this question, and, again, the only reason we have the luxury of asking this question is because the outcomes have improved so much in a relatively short period of time with the kinase inhibitors — imatinib, dasatinib and nilotinib.

And I just, lastly, want to make a plug for continued participation in clinical trials. What we do, what we've been able to accomplish would not have been possible without brave CML patients volunteering to participate in clinical trials and pave the way so that others may benefit.

So, with that, I will conclude my remarks and turn it back over to Carson.

Current Treatment Options for CML: **Progress in Research**

Question-and-Answer Session

Moderated by: Carson Jacobi, MPH

Thank you so much, Dr. Shah.

It is now time for the interactive part of our program.

We'll take our first question from the Web and the question comes from Pamela and she asks, "Upon initial diagnosis with CML, is there any way to determine how long the patient has actually had the disease and what in particular caused it?"

Michael J. Mauro, MD

We presume that once the patients present with symptoms of CML or signs of CML, they may have had their disease for a period of weeks, sometimes even a few months. CML is a slowly proliferating disease generally in the chronic phase and has a little bit to do with what brought some of the medical attention. Was it severe side effects, or was it serendipity? Someone had a blood test done for surgery or for another reason and they were noted to have a higher white count or abnormalities that led to the diagnosis. So it generally is a disease that has a prediagnosis phase of a few weeks or a few months in some cases. We don't think it could be something that went on for a very long period of time.

With regards to what causes CML, we touched on that, and we believe it to be a common genetic error in a rapidly dividing organ in the body and the marrow, but which takes hold and causes disease in a minority of patients. So, a common event with a much less common triggering of disease, there aren't in particular any risk factors that we know of that are clearly linked to CML except for, as I mentioned, high dose radiation and accident from nuclear exposure such as Nagasaki and Hiroshima during World War II.

Current Treatment Options for CML: **Progress in Research**

Operator

Thank you. Our next question comes from the line of Marguerite from New Jersey.

Caller: Marguerite

Good afternoon. Could you please address myelosuppression, it's treatment filgrastim long-term or reduction of dose? Could you also touch on its risks or just your general opinion if you were presented with a patient with long-term myelosuppression that won't resolve? Thank you.

Neil P. Shah, MD, PhD

So, this as I mentioned, can be an issue in a proportion of patients, hematologic toxicity, with all of the approved drugs. And this is one that if it occurs on one drug is, in general terms, likely to occur, unfortunately, on the other approved therapies. And what I think this most likely represents, at least in most patients, is perhaps a relative lack of normal stem cells. And so, the drug is clearly doing what we want it to do and it's reducing the number of cells that have BCR-ABL, but if the bone marrow environment doesn't have enough normal cells to pick up the slack, then we run into these issues where the blood counts continue to plummet.

Now, if that happens, you know, once, the first time we'll frequently try a brief dose interruption. We like not to withhold therapy for too long because the nature of the disease is such that we know that if we don't treat it, on average over a period of about 4 to 6 years, it will transform to a more aggressive phase that can only be cured by bone marrow transplantation. And I've, in fact, seen patients who had their dose held in such a fashion for a few months and then, unfortunately, during that period of time their disease did transform to a more aggressive phase.

Now, hopefully, that's a relatively rare occurrence, but, yes, we certainly try to maintain therapy with growth factor support if this tends to be a recurring problem. And although we would very much like to achieve a

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

complete cytogenetic response and a complete molecular response in every patient, I think there will, unfortunately, be people for whom the kinase inhibitors are not going to be able to achieve that.

Carson Jacobi, MPH

Okay, thank you, Marguerite for that question.

We have a question from the Web, and the question is, “What percentage of CML patients lose a positive imatinib response after 12 months of therapy or beyond? If a 3-log reduction is achieved, does that indicate a lesser likelihood to lose an imatinib response?”

Michael J. Mauro, MD

It all depends what type of response you had at 12 months. That would predict what your chances of losing response is.

If you took 100 patients in chronic phase and you started them on imatinib, at 12 months the majority of those patients would have a complete cytogenetic remission. For patients in complete cytogenetic, and that's, I'm talking somewhere in the neighborhood of 65%, 70% or beyond. Ultimately, 75% to 90% of patients receive a complete cytogenetic remission within the first 2 years of treatment. But at 12 months, that snapshot, again from the IRIS trial, the trial of newly diagnosed patients treated with imatinib, prior to its approval for front-line use, a 3-log reduction was achieved in about 40% of patients. A good minority will have a 3-log reduction and a majority will have a cytogenetic remission, and the risks of losing response in those patients is small.

There are a few patients who may have problems with tolerance, probably in the neighborhood of 5%. And there are about 5% total per year in the first few years that patients will either lose response or, unfortunately, see their disease relapse or progress. There is a smaller number of patients over time, so that's sort of the snapshot.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

With regards to the second part of the question about a 3-log reduction, I think I answered that part. It's really generally achieved in about 40% of patients at 12 months and there's significant improvement in protection and lowers the risk of relapse or progression further and, really, is the optimal level of response.

Operator

Thank you, our next question comes from the line of Mary from Illinois.

Caller: Mary

Yes, good morning, doctor. I have a question. I have a son that has CML and the only thing that I'm concerned about is if he bumps his leg or his arm, the skin pops open. And I know it's a blood disease, but why does it just crack open at such a slight touch or a tap?

Neil P. Shah, MD, PhD

Yes. I don't know if Dr. Mauro has any specifics to add. I mean, I will just say I haven't encountered that side effect in patients.

Now, if somebody's platelet count is very low and, as a result, either of the therapy or because they're having what we call myelosuppression or suppressed blood counts then, of course, people can certainly bleed very easily. But, as far as, certainly, we've seen slight changes in pigmentation where sometimes patients are maybe a few shades lighter than they were before they started taking the therapy, but perhaps Dr. Mauro has other information. I haven't seen this issue myself clinically.

Michael J. Mauro, MD

That's a side effect that I think probably isn't very well described or studied. Anecdotally, I've seen patients, generally a bit related to the dose, have increase in fragility of the skin. I think Dr. Shah's comment about the platelets is very appropriate. It's probably more likely to happen there but we do see some dermatologic

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

toxicity with imatinib: changes in hair, nails and skin in some patients. As Neil mentioned, hyperpigmentation or hypopigmentation is one, but I think fragility is another. It generally isn't a dangerous side effect but, clearly, especially you have a young, active young man, this might be more of a problem than someone who's leading a little bit more of a quieter lifestyle. So, I think just preventative measures are in line. But it certainly would be worth making sure there aren't any antiplatelet drugs or any other drugs that could potentially be contributing to the side effect and, of course, make sure the blood counts are stable.

Carson Jacobi, MPH

Okay, thank you, Mary, for the question. We have a question from the Web. It comes from Jean, and it's consistent with the side effect theme.

The question is, "What are your recommendations to deal with the imatinib side effects, such as diarrhea and bloating?"

Neil P. Shah, MD, PhD

Maybe you want to hear from both of us on this. Prior to the availability of the second-line agents, we used to do everything. I used to do everything possible to try to keep people on imatinib and that meant, of course, supporting any unpleasant side effects. We do know that, unfortunately, the side effect profile is not completely clean and there are people who have bothersome side effects that go on on a chronic basis. And we also know that this can, I'm sure, in some instances, lead patients to want to skip doses or to lower their dose. Even though it doesn't qualify as severe or life-threatening toxicity, it's obviously bothersome enough to the patient.

I think, at this moment, from what I have seen of the second-line agents, I believe that they are likely every bit as active as imatinib, and probably more so based upon some of the evolving data that's coming out of the previously untreated population. And so, in my clinical practice, I have a very low threshold to consider switching patients who have some unpleasant side effect on imatinib to either dasatinib or nilotinib. There's no guarantee that they will tolerate those drugs better but, you know, I take the approach of looking at this

Current Treatment Options for CML: Progress in Research

as something that, ideally, will be able to control this disease for decades. And getting a patient on whichever drug is best tolerated for him or her is, I think, absolutely essential to maximize the long-term compliance with the medication and outcome.

Michael J. Mauro, MD

I'll just add a brief comment. I think Neil answered that pretty completely. As Neil alluded to in his presentation, the cross intolerance is very low between agents. And I agree that with the availability of second-generation inhibitors, we should think about switching probably in such a patient. I've tried things, simple maneuvers such as Neil probably has used, such as antidiarrheal; fiber supplements actually are quite useful; they don't sound like they would be. But note that dasatinib and nilotinib, as well, both have some GI toxicity and have diarrhea [events] reported, so it's possible. But, interestingly, in trials, it was rare to have one type of intolerance to imatinib, cross over into ongoing treatment with the newer drug, but I don't know if we have as much detail on that particular side effect. So, I would work closely with your healthcare team and see if you could try supportive care, depending on the level of toxicity. If it's not effective, then really consider a switch.

Operator

Thank you. Our next question comes from the line of Deborah from Arkansas.

Caller: Deborah

I went off of imatinib for 6 months. We thought my liver had gotten bad and it was fat on my liver. I went back on imatinib, it's making me sick. I've had 5 blood transfusions. Should I be changed from imatinib?

Michael J. Mauro, MD

Sorry to hear about the specific problems you've had. We do know that liver toxicity is a potential risk for all of the drugs. It's probably a class effect, mainly because the drugs are metabolized to the liver. One of the

Current Treatment Options for CML: **Progress in Research**

things we often immediately want to address is whether there any other stressors or threats to the liver. And that would be important to look at when you've had that kind of toxicity develop.

That being said, it does seem like there are other things afoot and you're having some other common side effects that are also broad across the kinase inhibitors, meaning blood count reductions and you needing transfusions.

So, while liver toxicity might be one that wouldn't appear on a new drug if you switched, blood count toxicity, as Dr. Shah mentioned, has a higher likelihood of [appearing]. Clearly, patients in any situation really want to try to navigate to and find a therapy that offers the least risk, the least side effects, and the best chances for stable remission and ongoing tolerability.

We didn't address as much in this conference, but we need to find a therapy that fits, so compliance and adherence, meaning taking your medicine and sticking to it consistently every day, as possible. Not just from our interpretations and what we say as doctors, but from you as well being able to live with it.

So I would say it sounds like you're in a tricky situation and a switch might be warranted. Be aware that blood count side effects sometimes is below perfect, but liver side effects need to be carefully monitored and make sure your doctor is aware of anything else you're taking, including things that aren't prescribed. Sometimes medications or even nutritional elements can play a role in some of the side effects we see.

Carson Jacobi, MPH

Thank you, Deborah, for the question. We have a question from the Web. The question is, "If your PCR is negative for over 2 years, how often should you do the PCR test?"

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Neil P. Shah, MD, PhD

So, first of all, that's obviously a good sign if somebody is PCR undetectable. One thing that I like to always make sure of is that a patient who has a PCR undetectable test, at one point had a test that showed that they were actually detectable by the PCR.

Now, because of some intricacies that we don't completely understand, not every patient has a disease that can be monitored by the PCR test. But, assuming that you did, in fact, have a PCR test in the past that detected BCR-ABL and you now, for a 2-year period, have had no detectable level. I think, in the past we would try to do quarterly, every 3 months, PCR testing. I think given what we're seeing in terms of how stable these responses are, patients that achieve them, most of us are moving towards every 6 month testing.

I want to stress that, as I mentioned, I think the deeper the remission, in general terms, the better the long-term outlook will be. There will be exceptions to that. But I want to just stress that, unfortunately, at this time, despite the fact that you have been PCR undetectable for 2 years, I think it would be certainly a leap to believe that you are, in fact, cured; as much as I would love to be able to tell you that.

And so I would, as long as you're tolerating your medication, recommend you continue on whatever medication it is that's achieved that.

Operator

Thank you. Our next question comes from the line of Harriet from Tennessee.

Caller: Harriet

I'm having a problem. I have had to have some fluid removed from my back. It was a liter and a quarter of the fluid that was on my back, and the doctor said it was probably from the imatinib. I'm wondering, has this been a common occurrence or is this unusual?

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Michael J. Mauro, MD

I believe the term for what you had, based on what you're describing, is called a pleural effusion, and you had a thoracentesis, you had some fluid removed from the space between the lungs and the chest. So that is a side effect that can be associated with imatinib. It's not a frequent side effect.

We know that imatinib can cause swelling, fluid retention, in actually a fairly high proportion of patients. It tends to be more external, you know, around the eyes and the extremities, particularly the legs; and salt restriction can help minimize that, diuretics or water pills can help relieve it. When it's internal, it's a bit harder to manage.

I think that other factors may contribute as well. Some folks have tendencies to accumulate fluid related to their heart and their lung function or their anatomy/physiology. But, assuming all things have been looked into, that would probably be a reason to say that imatinib tolerance might be a problem if that were a recurrent issue. And, as we've both been speaking about, with newer drugs available, you might want to consider switching therapy, lest that happen again.

A careful decision, obviously, one to have with your healthcare team. But, in this case, looking at the alternatives, dasatinib and nilotinib, dasatinib has the same problem associated with it, probably to a bit of a higher degree. So, nilotinib would probably offer a more favorable side effect profile in this situation. But, again, something to bring back to your healthcare team and talk about in detail, but I suggest to raise the fact that it may be definitely imatinib-related and it may be reason to think about the long-term prospects on imatinib and whether a switch is warranted.

Carson Jacobi, MPH

Okay, thank you, Harriet, for the question.

We have a question, Dr. Shah, that's directed towards you, from the Web. The question is, "Dr. Shah, what is the state of nonkinase inhibitor therapy for CML? Example, vaccines, etc."

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Neil P. Shah, MD, PhD

So, there is more beyond kinase inhibitors for the treatment of CML. And, of course, before we had the kinase inhibitors, really, we had a therapy that I think we have to bear in mind was, in fact, curative for a small proportion of patients, a very small proportion, and associated with a fair amount of side effects, and that was interferon. And that is something that I think, because of the fact that there are patients who took interferon for a defined period of time, maybe 1 or 2 years, back in the early 1990s, who've taken no further therapy since, who have no detectable CML all these years later.

So, I think we, of course, should remember that interferon has curative potential. We don't understand a lot about how it does that but one of the things that has been tried, of course, is to combine interferon and more long-acting interferon, which may be better tolerated than the old-fashioned interferon, to combine that with imatinib in clinical trials. And there was a study presented by the French group that basically compared combining interferon, a long-acting interferon with 400 mg of imatinib to 400 mg of imatinib alone, and also to 800 mg of imatinib.

And one of the noteworthy findings of the study was that the likelihood of being PCR undetectable, I don't remember, I think it was after 2 years, the likelihood of being PCR undetectable was twice as high in patients who were treated with imatinib and interferon.

Now, while that sounds good, fully half the patients, approximately half the patients, had to discontinue the interferon therapy, even though this is the long-acting interferon that is supposedly better tolerated. But, so that's one nonkinase inhibitor approach.

There are, as I mentioned in one of my slides that I perhaps didn't explain, SMO or smoothed inhibitors. These are pathway inhibitors that may be particularly of use in CML stem cells. So, these try to eradicate what may be an especially important survival mechanism of CML stem cells. So, this is something that is on the horizon.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Now your question specifically had to do with vaccine therapy. And partially because of the interferon experience, which we know is an immunomodulatory agent, partially because of our experience with transplant, we have a good sense that immunotherapy is actually something that the immune system could potentially have the ability to impact the disease. And so people have developed vaccines related to BCR-ABL because diffusion of BCR-ABL is an abnormal thing that we should not have. And so people have been working on that for a number of years.

And, unfortunately, one of the difficult things with determining how these are doing is that comparative studies have been lacking. What I mean is where you take patients and you divide them in half. Half of them you vaccinate, the other half you just continue on therapy.

The reason that's a critical question is we know that just continuing imatinib alone in patients will lead to deeper responses in a cohort of patients. And so, there was an update from an Italian study on vaccines during this meeting, where they basically reported that 50% of patients who started vaccination, typically, about 18 months or so after starting imatinib; and these were patients who were already in a complete cytogenetic response, that about 50% of these patients had a 50% or greater reduction in their BCR-ABL transcript level.

So, I think this is an area that has been kind of plodding along for a number of years; no clear role for it yet, but I think still something that deserves investigation.

Operator

Thank you. Our next question comes from Sharon from Pennsylvania.

Caller: Sharon

Just a couple quick questions. Dr. Mauro stated that the quality of the stable [response] is important. Would it be best to draw the bloods on certain days, assuming that labs are going to either be busy or weekends come into play, those kinds of things?

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

And the other thing is, after reaching and maintaining zero detectable for a while, I went through a period of a lot of stress and I lost the response slightly. It wasn't major, still had 3-log. Does stress contribute to this and make it harder, or is just like every other disease?

Michael J. Mauro, MD

Those are some great thoughts. I think, with regards to PCR testing, many of you might wonder, why do we use the blood and not do it on the marrow when we're in there assessing response? First of all, the likelihood of needing to examine the marrow for the reasons we would, to look at the pathology to examine cytogenetic, becomes less important quickly over time, so we use peripheral blood. And the blood is immediately, or should be, generally, for PCR testing, put into media, or into a solution basically that will allow the extraction of DNA RNA efficiently, even after a period of time.

As you might imagine, transit time conditions will affect the sample so, if you can, having blood drawn at a site. For example, my patients come to my center and have the blood drawn and it's sent right to the laboratory for processing. The results are optimal, but we look carefully at, for example, patients who live at a distance or others who are seen by their physicians who use our laboratory, and the transport of samples by, you name it, an overnight carrier and the post office and other carriers works. So, it doesn't have to be drawn on a certain day necessarily. It doesn't affect it as much.

And then the second question was, part of your question was about stress and losing molecular response. I wish I had the answer to that because I think I anecdotally hear a lot of patients tell me, they think they were diagnosed or their CML occurred at a time of stress.

There are other lines of research around emotional and psychological states and support and lack of support and how it might affect cancer therapy course or outcome. I wouldn't say it's something we know a lot about. I wouldn't blame it though.

I think what's probably more important to point out that, I think Neil has mentioned and, hopefully, I mentioned as well, what we believe the state-of-the-art in CML is that you can exquisitely control the CML

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

down to a very small level. And I repeatedly when counseling my patients, I see that a PCR that's undetectable today means it's below the radar. And if our radar screen just widens or broadens just a little bit, the sample we draw 3 or 6 months later might not be undetectable. It might be detectable again. And if it's at a small enough level, they may not have been a change in the disease, it may have been a change in the sensitivity of the test, or a very small change in the disease.

So, although there is a lot of anxiety around ongoing molecular testing and maintaining or not maintaining molecular response, it's not uncommon for patients to have small levels of fluctuation.

There's some research at this year's ASH looking at this, what's the pace of response? And researchers at Novartis actually had shown different slopes or different rates of decline of leukemia cells. And there's probably, in the end, or the later parts of treatment, a much slower rate of decline. And there may even be fluctuation.

So, that being said, we can certainly, hopefully, either repeat or investigate when we have a concern that there is a rise in PCR. There's been some very good work around subtle changes that potentially could predict for resistance or mutations, but I can tell you that the majority of the time it tends to be fluctuation than true relapse or loss of response. And the larger datasets or research in stable remissions on large trials of imatinib really support that; that we don't see patients subsequently lose their response.

So, of course, don't get stressed out and try to stay as healthy as you can otherwise, but don't blame yourself necessarily for that. And with good PCR testing, we should really be able to track from its progress and sometimes we have to recheck and potentially sweat out what might be a questionable value, but that's the importance of staying close and being monitored carefully.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Carson Jacobi, MPH

Okay, thank you, Sharon, for that question. We have a question from the Web. And the question is, “What causes continuing low red blood count in imatinib-treated CML after a complete molecular response is achieved?”

Neil P. Shah, MD, PhD

That’s an excellent question. And, you know, I think, certainly from my clinical experience, I’ve seen that. And I have a patient who’s been in complete molecular response for several years and she wanted to stop imatinib and see if that improved her hemoglobin, and it actually did rather substantially.

So, I think, while we don’t think of these drugs as being largely myelosuppressive, I think we have to keep an open mind. But, of course, it needs to be proven that there is no other cause of the low hemoglobin. So, if you haven’t had a colonoscopy, that should be performed. Certainly, tests looking for iron deficiency, other potential medical causes before assuming that this could, in fact, be due to the imatinib. But I certainly have seen it occasionally as a side effect of imatinib.

Operator

Thank you. Our next question comes from Francis from North Carolina.

Caller: Francis

Thank you. I’d like to thank both doctors for an excellent presentation as well as to their outstanding work in CML.

I have a question concerning reporting PCR on the international scale from lab to lab. Most labs now are supposedly using the international scale so the results of PCR can be comparable.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

I had a bone marrow at 6 months that showed complete cytogenetic response. The PCR on the international scale at the Mayo Clinic revealed 0.2%. And, of course, 0.1% is considered a major molecular response. My local hematologist sent another specimen to a New Jersey lab and this showed PCR-U (PCR-undetectable).

Now, to my mind, this would, all other things being equal, indicate that the latter lab did not have the sensitivity to report the comparable level. And I was wondering, is there a standardization available, say, from the American Society of Clinical Pathologists or something, where unknown samples can be sent to see if the labs are also comparable on that basis?

Thank you.

Michael J. Mauro, MD

That's an excellent question. And you described some of the dilemmas that we face with regards to molecular testing in CML.

The first point you made about one laboratory showing probably a near 3-log reduction and the second lab showing an undetectable status may reflect exactly what you've said. In that, when the sensitivity of the lab isn't up to snuff or really up to its peers, the likelihood of an undetectable value is dramatically increased and it sort of casts the suspicion on the CMR or the PCR-U category of response.

To be clear though, that level has been defined by the collaboration of laboratories, what is a complete molecular response? It represents the 4.5-log reduction in BCR-ABL transcripts.

There is a very active collaboration going on worldwide looking at a yardstick, basically, we can use to measure PCR responses and, intuitively, it would start at 100%, when you're untreated. You've alluded to your response particularly on that scale.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Laboratories that would adapt that scale, they should be able to normalize their results to that scale. They may not be able to have sensitivity down in the lower ranges though. That really is reliant on the assay and the technique and some of the tools that little different laboratories use. So we're hopeful that very soon we'll at least have all laboratories reporting their results on an international scale.

What the second piece of information needed is, what is the sensitivity of the lab? And, actually, more importantly what was the sensitivity of that assay? Because it's not just about the lab, it's also about, whether the sample is reliable?

For example, in our laboratory, if we can't report a certain level of sensitivity, we shouldn't report the value because if it's an undetectable value, for example, like what you experienced, what reliance can we place on it?

So, more work is needed. Look for, hopefully, global adaptation of the international scale so we can speak the same language.

Secondly, we need all labs to say what is their sensitivity. And, of course, as patients, or all of us as healthcare providers, we need to question when we see differences or when we see a new status change, a) we'd want to confirm it, b) make sure that it's reliable.

Current Treatment Options for CML: **Progress in Research**

TRANSCRIPT

Closing Remarks

Moderated by: Carson Jacobi, MPH

Okay, Francis, thank you for your question. And, actually, thank you all for your questions. Our program has come to a close.

If you can please help me thank again, Dr. Mauro and Dr. Shah, for such informative presentations. So, on behalf of *The Leukemia & Lymphoma Society* and everyone on the phone, we would like to thank you for all the work that you do every day in supporting patients and their families touched by cancer. And we appreciate that you gave of your time to us today. And for all of you, if your questions weren't answered, our Information Resource Center is open and our specialists are available to answer your questions. The number is 1-800-955-4572.

So, on behalf of *The Leukemia & Lymphoma Society*, Dr. Mauro, Dr. Shah and I, would like to thank you all for joining us. Goodbye. We look forward to the next program. We wish you well.