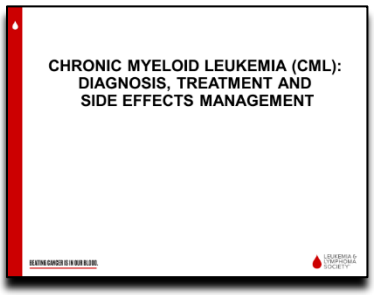
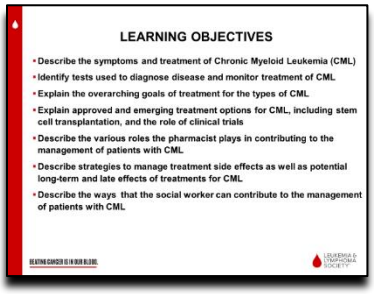


Slide 1 - Chronic Myeloid Leukemia: Diagnosis, Treatment, and Side effects Management

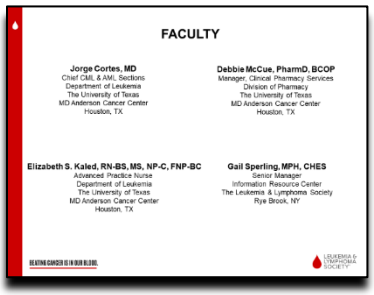
Lauren Berger: Hello, everyone. On behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us for this continuing education program on chronic myeloid leukemia: diagnosis, treatment, and side effects management.



Slide 2 - Learning Objectives

The learning objectives for this program are listed on this slide:

- Describe the symptoms and treatment of Chronic Myeloid Leukemia (CML)
- Identify tests used to diagnose disease and monitor treatment of CML
- Explain the overarching goals of treatment for the types of CML
- Explain approved and emerging treatment options for CML, including stem cell transplantation, and the role of clinical trials
- Describe the various roles of the pharmacists plays in contributing to the management of patients with CML
- Describe strategies to manage treatment side effects as well a potential long-term and late effects
- Describe the ways that the social worker can contribute to the management of patients with CML



Slide 3 - Faculty

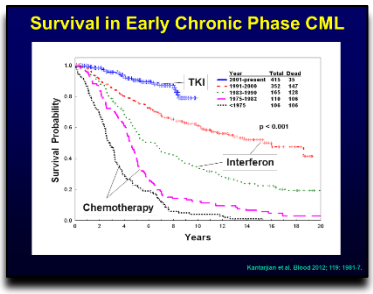
We're fortunate to have as our presenters, Dr. Jorge Cortes, one of the nation's leading experts in chronic myeloid leukemia and his colleagues, Dr. Deborah McCue, a clinical oncology pharmacist, and Elizabeth Suzan Kaled, an Advanced Practice Nurse, as well as Gail Sperling, Information Specialist. We appreciate their dedication and their commitment to caring for patients living with blood cancers.

Dr. Cortes is Chief, CML & AML Sections, Department of Leukemia, at The University of Texas, MD Anderson Cancer Center, in Houston Texas. Deborah McCue, is Manager, Clinical Pharmacy Services, Division of Pharmacy, at The University of Texas, MD Anderson Cancer Center. Elizabeth Kaled, is an Advanced Practice Nurse in the Department of Leukemia, at The University of Texas MD Anderson Cancer Center, in Houston and Gail Sperling is Senior Manager, Information Resource Center at The Leukemia & Lymphoma Society.

Our special thanks to Dr. Cortes, Dr. McCue, Nurse Kaled and Information Specialist, Ms. Sperling for volunteering their time and expertise with us. Dr. Cortes, I am now privileged to turn the program over to you.

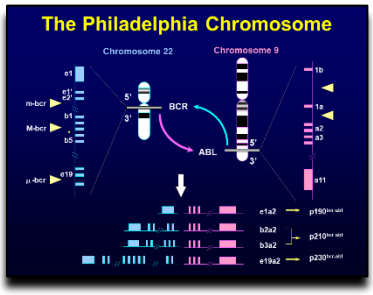
Slide 4 - CML - State of the Art

Jorge Cortes, MD: Hello, my name is Jorge Cortes from the Department of Leukemia at MD Anderson Cancer Center. We're going to be talking today about some of the current understanding on the diagnosis, monitoring, management, and treatment of patients with this disease.



Slide 5 - Survival in Early Chronic Phase CML

And I'd like to start by reminding the audience that one of the big achievements in cancer has been the management of chronic myeloid leukemia. The survival of patients is greatly improved over the years. The first major breakthrough was the introduction of interferon, and with that we already saw a significant probability of survival compared to what we were seeing with chemotherapy with busulfan and hydroxyurea. But, certainly, with the introduction of tyrosine kinase inhibitors, this has changed dramatically, to the point that whereas in the past the median survival for a patient with newly diagnosed chronic phase CML was about 4 to 5 years, now after 10 years we have not yet reached the median survival, and 80% to 90% of patients are expected to be alive at that point.

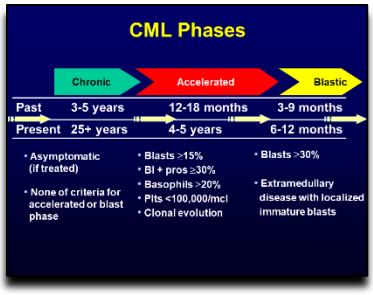


Slide 6 - The Philadelphia Chromosome

It all started around 1970 when it was first identified that patients with this disease had a minute chromosome 22, that later was recognized as representing a balanced translocation between chromosomes 9 and 22, what we now call the Philadelphia chromosome.

And that puts together 2 genes, chromosome 22 has BCR, and chromosome 9 has ABL, which have a break somewhere, within the gene, and that creates a chimeric gene that we call BCR-ABL. But there are different breakpoints that can occur. The most typical ones in CML are what we call the breaks in the major breakpoint across the region of BCR and can produce 2 typical products. One is called B2a2, which in the mother nomenclature we call E13a2 and B3a2, which now we call E14a2.

These, as I said, are chimeric genes that translate into a protein that has a constitutive activation of the kinase of ABL. So that is constantly turned on and leads to increased proliferation, decreased apoptosis, etc.

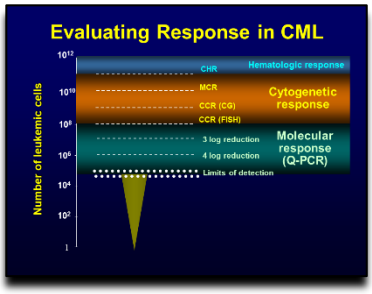


Slide 7 - CML Phases

In CML, patients typically progress through 3 different stages of their disease or, as we call them in CML, 3 different phases of their disease. The great majority of patients, particularly today, over 85% to 90% of patients are diagnosed in what we call the chronic phase. Historically, as I mentioned, had a median survival of 3 to 5 years. Now this is much longer.

It was believed that if patients are not treated, everybody would eventually progress to the end stage of the disease, the last stage which we call the blast phase, which has a very poor prognosis and is very similar to an acute leukemia.

And about two-thirds of patients progress from the chronic phase to the blast phase through an intermediate phase that we call the accelerated phase, which is starting to show changes in the blood or in the bone marrow that tells that the patient is starting to move towards the blast phase, although not yet there. So, we may see an increased number of basophils or blasts or addition of chromosome changes, etc.



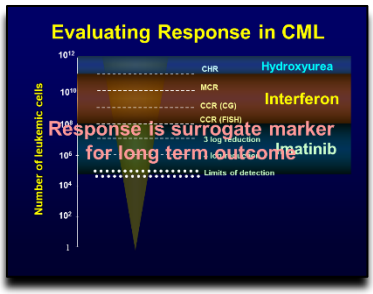
Slide 8 - Evaluating Response in CML

When we assess a patient at the time of diagnosis, we estimate that a patient will have approximately 10^{12} leukemia cells in their body. Once we start treatment, the first thing that we try to achieve is what we call a hematologic response. That means that the blood parameters now look normal, that if there was any splenomegaly, this is reduced back to normal size, etc. That is important, but that still leaves many leukemia cells behind. We think that at that time, the patient may still have somewhere around 10^{11} leukemia cells. So still, significant amount of leukemia left.

We then try to achieve what we call a cytogenetic response. That means that through assessment of the chromosomes, either by a routine cytogenetic analysis or by FISH, we do not see the Philadelphia chromosome anymore. That is, again, what we call a cytogenetic response and that is very important. That's probably the gold standard of a good response in CML, but it still leaves a lot of disease behind.

As our treatments have improved and as our molecular techniques for monitoring patients have advanced, we now aim to achieve what we call molecular response. And that is that by using a PCR, we can detect as little disease as possible, and at some point, we can go to undetectable disease.

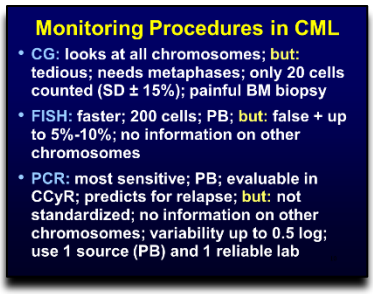
Now it is important to recognize that even the PCR has a limit of detection. So, once we are below the limit of detection, we call it undetectable because we don't know if it is just below that level of detection or it's truly disappeared. [1]



Slide 9 - Evaluating Response in CML

Now we can correlate these aims of therapy through the different therapeutic eras, from hydroxyurea, where all we could achieve was a hematologic response; interferon, when we, for the first time, started achieving cytogenetic responses, and now with imatinib and other tyrosine kinase inhibitors where we aim for these deeper molecular responses.

But it is very important to remember that these responses are surrogate markers for the long-term outcome. The response is not the aim by itself. We value them because they mean something for the future, and I'm going to talk about these more, later in my talk.



Slide 10 - Monitoring Procedures in CML

Before that, I want to talk a little bit more about these different techniques that I mentioned that we use for monitoring. The first is the cytogenetic analysis which is the oldest available technique and is very valuable. It is very important because it looks at all the chromosomes. So, it allows us to identify chromosomal abnormalities in other chromosomes which occur in some patients, so that is very important to do at diagnosis for sure and sometimes during the course of therapy.

However, the problem is that it is a difficult procedure. It's very tedious. It has to be done in the bone marrow. It is not always possible to grow cells in the laboratory to get them into metaphase, and it has a low sensitivity. It only counts 20 cells.

FISH provided an advantage because it's a faster test that can be done in the peripheral blood, and it can count up to 200 cells. But it does have some false positives, and it does not provide any additional information on some of the other chromosomes. And, PCR is very important because it's the most sensitive technique, it can be done in the peripheral blood. It can provide information even after a patient has achieved a complete, cytogenetic response.

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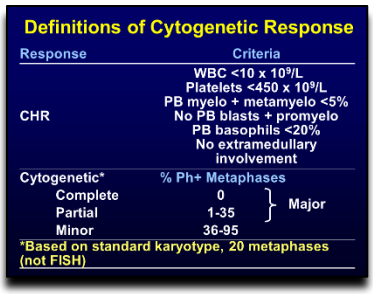
1 See appendix, at end of document, for table from Chronic Myeloid Leukemia booklet -- Source: www.LLS.org/booklets

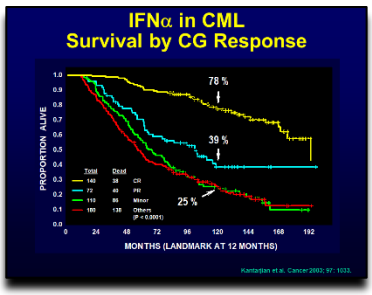
The main problem with PCR is that it's still a very specialized test, which has a lot of variability between different labs. It is not well standardized, but we've made a lot of progress on these already. But because it has many steps, it is prone to errors and contamination and other things.



Slide 11 - Definitions of Cytogenetic Response

I also want to review the criteria for response. The hematologic response, as I mentioned, essentially means that the peripheral blood goes back to normal, that we don't have extramedullary involvement, no spleen, etc.

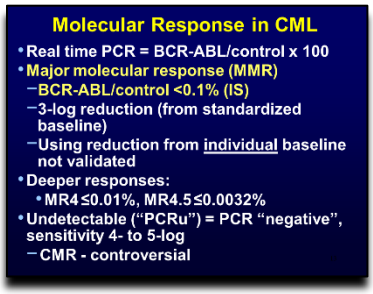
The cytogenetic response means that we do not see the Philadelphia chromosome. The criteria are meant to be with a standard cytogenetic analysis, but we frequently extrapolate to FISH. So, if we don't see any more Philadelphia chromosomes, we call that a complete cytogenetic response. If we see up to 35% of the Philadelphia chromosome, we call that a partial cytogenetic response. Anything below that is a minor response.



Slide 12 - IFNα in CML: Survival by CG Response

This is very important; and, as I mentioned, the complete cytogenetic response is the gold standard for a good response. And that comes back from the days of interferon where, as you can see on this graphic, we established that patients who achieve a complete cytogenetic response, after 10 years, 80% of these patients, almost 80% of patients, are still alive.

So, that established that this response correlated with a very dramatic improvement in survival. The problem was that with interferon, this was very difficult to achieve. Only a small fraction of patients can get to that kind of response. But it became promptly, very quickly the aim of therapy.



Slide 13 - Molecular Response in CML (See Appendix 2 at end of transcript for further explanation of the International Scale)

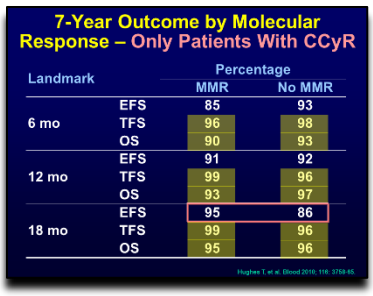
Molecular responses are important, because we can get, as I mentioned, deeper, more valuable responses that go well beyond the level of detection of the cytogenetic techniques. So, this makes it into an evaluation of minimal residual disease.

The levels that we aim for are the major molecular response. That was the first one that was important. And, importantly, the molecular response, what it is telling us, is a ratio between BCR-ABL, that chimeric gene that I described earlier, in relation to a control gene. Very frequently we use ABL, but other genes can be used.

And you assess that, and if you have less than 0.1%, we call that a major molecular response. So, there is BCR-ABL represents less than 0.1% of the amount of the control gene that you see on that patient.

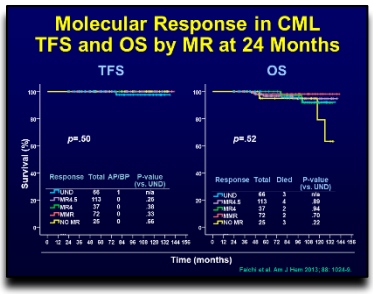
So that, essentially, is a 3-log reduction from the baseline. The baseline, grossly we considered that is 100%. And as we have gotten to better therapies and this technique has gotten better, we have defined deeper responses. For example, we call MR4 when we get to 0.01 or less. Remember, a major molecular response or MMR is 0.1. So, it would be MR3, 3 logs, and MR4 means 4 logs. And MR4.5, which we can see there's sort of like the deepest molecular response is 0.0032 or less. That's 4.5 logs from the baseline.

Many times, we talk about undetectable, as I talked about earlier. Some patients call it PCRu, some people call it PCR-negative. The problem with this is that it's difficult to define the sensitivity of the test and how deep you go, and it's much more difficult to standardize. That's why we've come to an agreement that the lowest that we can standardize is that MR4.5, and that is a very good goal for therapy nowadays in many ways.



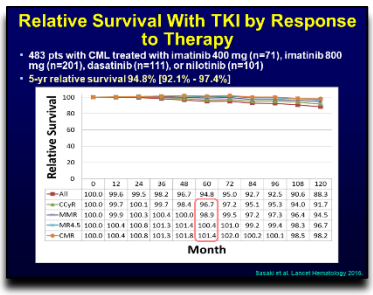
Slide 14 - 7-Year Outcome by Molecular Response – Only Patients with CCyR

Now what do these molecular responses mean? I already explained that a complete cytogenetic response correlates with an improvement in survival. So, if you now look at all the patients that have achieved a complete cytogenetic response, and then divide them by those who achieve a major molecular response and those who do not achieve a major molecular response, we see that if they, the patients who achieve a major molecular response by 18 months, they have an improvement in event-free survival. That means that they have a much less likelihood of progressing to the advanced stages, accelerated or blast phase, or even losing their response to therapy. They do not have a benefit in survival. They do not have a benefit in transformation, but they do have a benefit in that event-free survival if they, in addition to their complete cytogenetic response, have achieved a major molecular response.



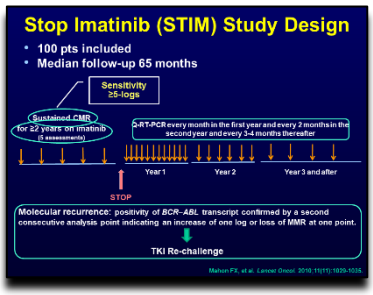
Slide 15 - Molecular Response in CML: TFS and OS by MR at 24 Months

Now what about the deeper molecular responses? Well, as you can see from these graphics, again, once you achieve a complete cytogenetic response, these deeper molecular responses do not really have a benefit in survival or in transformation-free survival. I will talk about some of the other benefits that you get with these deeper molecular responses and why we are interested in achieving these deeper responses.



Slide 16 - Relative Survival with TKI by Response to Therapy

But before I get to that, one thing that I want to emphasize is that by achieving all these good responses in the overwhelming majority of patients, what we have determined is that patients today diagnosed with CML have a near normal life expectancy, particularly those who have a good response to therapy. That means that a patient that has CML, that is properly managed, and that has good access to treatment, is likely to live as long as other individuals of the same age and sex, etc, and they're not going to die of leukemia. So it is very, very important then that we are able to treat them properly.



Slide 17 - Stop Imatinib (STIM) Study Design

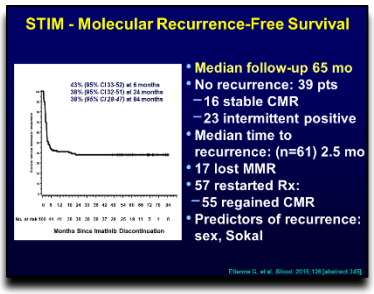
For many years, since we started treating patients with CML, we always advised patients that this was treatment for the rest of their lives. And that is not a bad thing because, considering that we're treating cancer, if you can survive and not die of your cancer by taking a pill a day, that is really a very good thing; and we wish we had that for many other cancers.

But what if we also could stop treatment at some point? So, there was a pivotal trial, a study that I'm showing here called the STIM trial where patients that had a sustained response were offered treatment discontinuation.

Now I want to emphasize what patients were included in these trials possibility. First of all, they had to have, as I mentioned, a sustained complete molecular response. And here they defined complete molecular response as negative PCR with a very sensitive PCR, a 5-log detection. That's something that is not easy to achieve in most of the clinical laboratories.

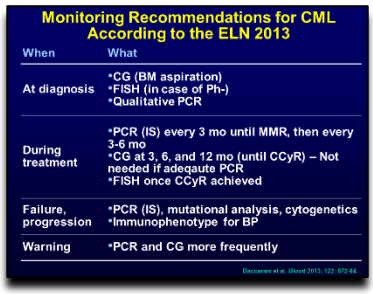
And then they required that patients had shown these complete molecular responses for 2 years in a row with assessments at least every 6 months, meaning at least 5 assessments that were all negative for PCR.

So, if they met that criteria, they offered discontinuation, and then they monitored the patients closely. Every month for the first year. Every 2 months for the next year. And after that every 3 to 4 months. And, if the patient showed that the PCR became detectable again, they started TKI once again.



Slide 18 - STIM - Molecular Recurrence-Free Survival[2]

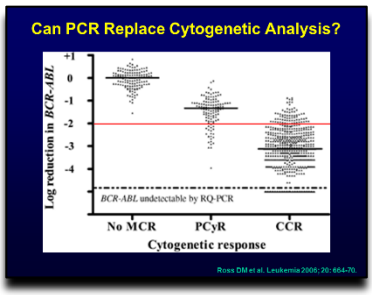
For these patients, the results showed that about 40% of patients have remained without having to resume therapy. The follow-up is long. And when you look at the shape of the curve that I'm showing on the left of this slide, it is remarkable that the overwhelming majority of the patients who lose that response and have to resume therapy, do so in the first 6 months. There's a few others, a few, but some, in the next 18 months, so up until month 24. After 24 months, very few patients lose their response. There have been some; not on this study but in other studies. But the risk significantly declines after 24 months.



Slide 19 - Monitoring Recommendations for CML According to the ELN (2013)

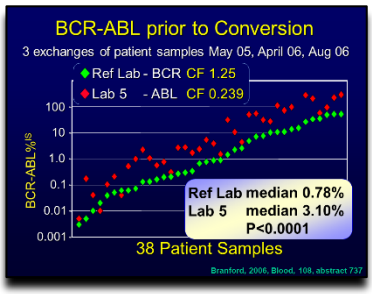
So, we followed that. What we recommend is that every patient at the time of diagnosis has to have a bone marrow aspiration. That is critical. We want to see all the chromosomes to understand where the patient is starting. And we want to check FISH and PCR mostly to know that all of these tests can detect the particular breakpoint that the patient is having, the type of rearrangement. There are some patients that have unusual rearrangements that they'd not be identified by these other techniques. And that is important to recognize from the beginning.

Then we monitor patients with chromosome analysis, which means a bone marrow aspiration at least, at 6 and 12 months, perhaps at 3 months, until they achieve a complete cytogenetic response. After that, you probably don't need too many bone marrows, unless you're changing therapy. And then, with a PCR every 3 months until they achieve this major molecular response. Then every 3 to 6 months.



Slide 20 - Can PCR Replace Cytogenetic Analysis?

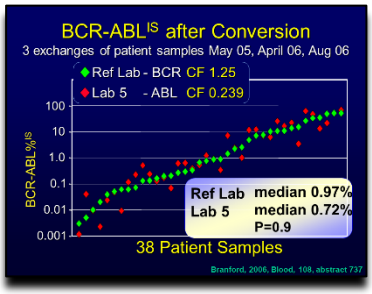
It is important to mention that there is good correlation between the PCR and the cytogenetics, although the correlation is not perfect. In general, patients that have a complete cytogenetic response have levels of less than 1% by the PCR, and patients that have a partial cytogenetic response have levels of less than 10%. But there is some overlap between these levels.



Slide 21 - BCR-ABL Prior to Conversion

Just the last thing that I want to mention about the monitoring is that, I mentioned that this is a technique that has been difficult to standardize. If you run the same test in two good laboratories, you may obtain different values between the two laboratories. So that's what was done in this experiment that I'm showing you on this slide. The same sample was run in 2 laboratories – one shown in green, the other one in red. And you see the curves are similar, but one consistently showed higher results than the other.

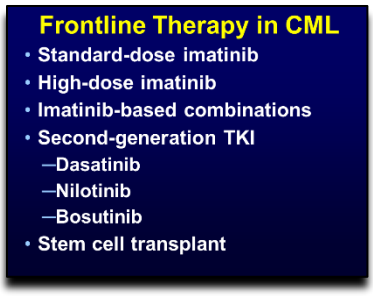
[2] Sokal Scoring System - A scoring system used for patients with chronic myeloid leukemia that estimates their survival. Patients are rated low risk, intermediate, or high risk based on their spleen size, platelet count, age and blast count. It is also used to predict the response to tyrosine kinase inhibitors (TKIs). TKIs are a type of drug used to treat CML. See Glossary on www.LLS.org



Slide 22 - BCR-ABL After to Conversion

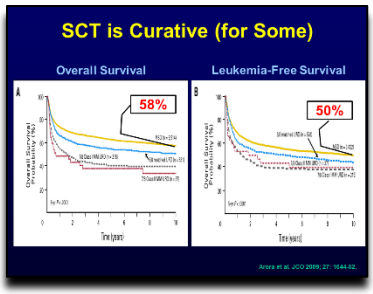
So, the question was, can we normalize these so that we can then give a conversion value so that you could then see pretty much the same result between the two labs. So with that conversion, you would see the curves look like that.

One result would talk to the other, in most instances. So that is what the international scale is, has established a conversion factor so that when you go from one laboratory to another you're getting approximately the same results and can understand what has happened. That is not perfect yet, but we're getting much closer to that.



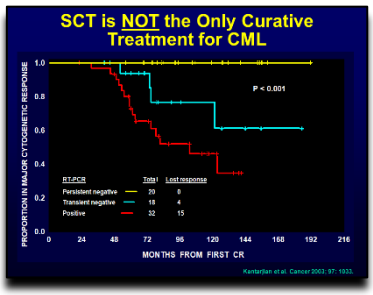
Slide 23 - Frontline Therapy in CML

All right, let's talk a little bit about the frontline therapy. In 2000, the imatinib was introduced, 2001, was introduced as initial therapy for CML and has remained the standard therapy since then. There have been, then after that, some investigation into higher doses of imatinib and combinations based on imatinib. But then the second-generation tyrosine kinase inhibitors came. And today we have 3 second-generation tyrosine kinase inhibitors that are approved, also, as initial therapy for CML – dasatinib, nilotinib, and more recently bosutinib. So, these are all frontline strategies that can be used for patients. Transplant had been so for many years, but now it's rarely used as initial therapy.



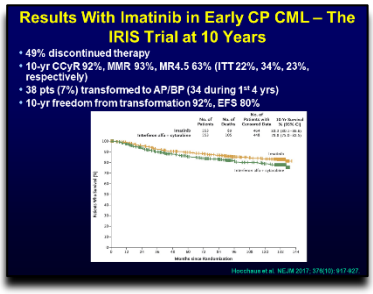
Slide 24 - SCT[3] Is Curative (for Some)

Now, I want to remind you that transplant remains a valued option. We don't use it much as a frontline therapy, but it is still a valued option that we use in patients who have received several tyrosine kinase inhibitors without a response. But we need to remember that it can be curative in some patients. Not in everybody. Some patients relapse, of course, it also has mortality, but it is an option that we have to remember.



Slide 25 - SCT Is NOT the Only Curative Treatment for CML

But we also have to remember that transplant is not the only curative treatment for CML. Even from the days of interferon, which is what I'm showing you on this graphic, we had some patients that would reach these PCR undetectable levels. And when you see those patients, the yellow curve, and you see what's happened today in more than 10 years, and most of these patients have actually stopped interferon, they have not relapsed. So those patients are cured. The problem, of course, is that with interferon, those were very few, but now we have much better treatment.



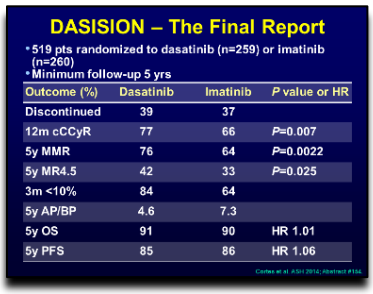
Slide 26 - Results with Imatinib in Early CP[4]-CML – The IRIS Trial at 10 Years

All right, well those better treatments are the tyrosine kinase inhibitors, and this is imatinib. As I mentioned, that was the first one that was introduced as first-line therapy. This came through a pivotal trial called the IRIS trial where imatinib was compared to interferon plus Ara-C (cytarabine), which was the standard of care at the time.

And these are the results after 10 years of follow-up. And, we know that the results were outstanding, very high rates of complete cytogenetic response, more than 90%. And even these deeper molecular responses, MR4.5, occurring in more than 60% of the patients. And you see the survival curve, at the bottom of the slide, showing a benefit for imatinib. Even when patients started with interferon, really most of these patients very promptly

[3] SCT - Stem cell transplantation
[4] CP: Chronic Phase

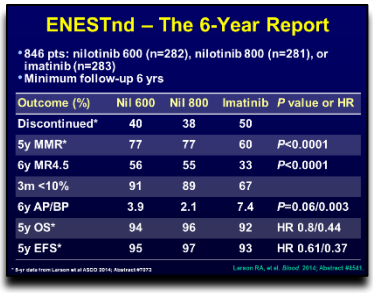
crossed over to imatinib because they were showing a poor response or poor tolerance to therapy. But even with that crossover, it is showing that starting with imatinib is better for survival.



Slide 27 - DASISION – The Final Report

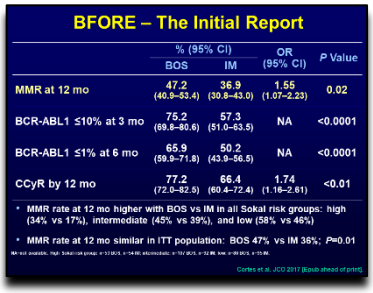
As I mentioned, then came the second-generation tyrosine kinase inhibitors, and I'm going to show you 3 slides in succession, of the 3 randomized trials that led to the approval of these drugs. All of these studies used the second-generation tyrosine kinase inhibitor and randomized, compared to imatinib. And the summary can be, that in all instances, in all 3 studies with all 3 drugs, there was an improvement in their response rate. We got earlier responses with the second-generation TKI. We got deeper responses. We got faster responses. We got fewer transformations to accelerated phase and blast phase. We haven't yet seen an improvement in overall survival or progression-free survival. But, number one, it's only about 5 years of follow-up at most, which may not be enough. It took 10 years to show that with imatinib compared to interferon, even though the difference between those two therapies is much larger.

And, number two, related to that is that with imatinib, we already have very good survival. We have very good rates of complete cytogenetic response, and so it'll be very difficult to show a meaningful improvement in survival, but we do have these other benefits. So, in this slide is the data with dasatinib, showing what I summarized just a few minutes ago.



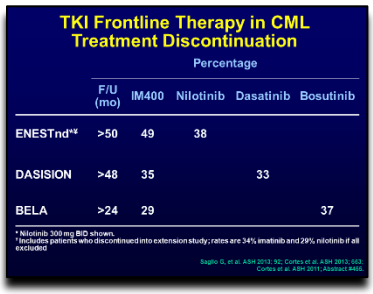
Slide 28 - ENESTnd – The 6-Year Report

Then, this is the study with nilotinib, compared to imatinib. In this study, two different doses of nilotinib were investigated, and the lower one was as good as the higher one, so we used the lower one for initial therapy. That is 300 milligrams twice daily, again, showing more responses, deeper, faster, etc.



Slide 29 - BFORE – The Initial Report

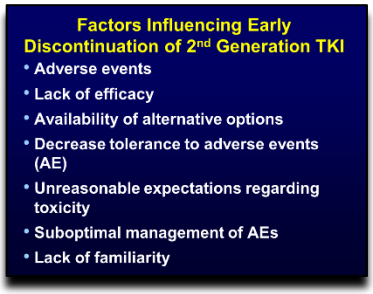
And then, this is the most recent study. This is the BFORE study with bosutinib versus imatinib. And, this is a much younger study, so, all we have now is the 12-month follow-up; but it's already showing these deeper responses and faster responses, and more responses, etc. So, again, all these 3 drugs – dasatinib, nilotinib, and bosutinib – are approved frontline therapy for CML.



Slide 30 - TKI Frontline Therapy in CML: Treatment Discontinuation

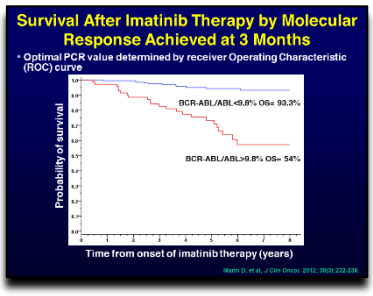
Now one of the problems that we see is that despite their success and generally being well-tolerated, perhaps better than imatinib in many ways, we see that a lot of patients have discontinued therapy with any of these drugs. That's about a third of patients or maybe even a little bit more.

That is a problem because if these drugs are much more effective than imatinib, and they are well-tolerated, why are patients discontinuing therapy at such a high rate? You would expect much fewer treatment discontinuations.



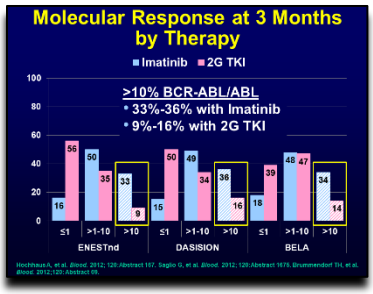
Side 31 - Factors Influencing Early Discontinuation of 2nd Generation TKI

Certainly, sometimes that happens because of adverse events or because of lack of efficacy. But I think part of what's happened is that because we have other treatment options, we tend to change treatment a little too soon. We accept, or we're less willing to manage adverse events, or we have unreasonable expectations about toxicity. We expect these drugs to have no side effects and we, perhaps, need to be cautious with that. I think most patients can manage their treatments if we help them with managing their adverse events.



Slide 32 - Survival After Imatinib Therapy by Molecular Response Achieved at 3 Months

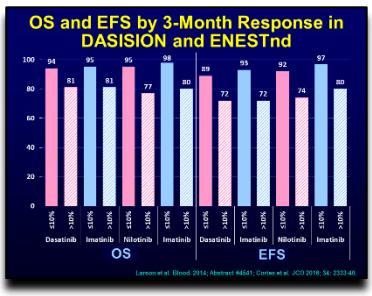
One important thing that we recognize is that early responses at 3 months are very important, and a value of the PCR of around 10% correlates with a much better prognosis. So, you see here on this graphic that patients that are less than 10% at 3 months have a much better probability of survival than patients that have a higher value, more than 10%.



Slide 33 - Molecular Response at 3 Months by Therapy

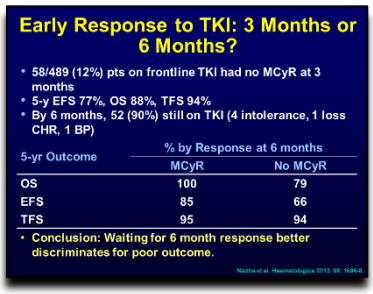
Well, in the 3 studies that I mentioned, the nilotinib, dasatinib, and the bosutinib studies, what we have seen is that the patients that are treated with imatinib, grossly about a third of patients have more than 10% transcripts at 3 months.

But the patients that are treated with the newer drugs, nilotinib, dasatinib, or bosutinib, only about 10% to 15% of patients fall behind in their response that way. So, clearly, you get a benefit by getting these, deep, earlier responses, as I mentioned earlier.



Slide 34 - OS[5] and EFS by 3-Month Response in DASISION and ENESTnd

And that is important because this correlates with an improvement in overall survival and with event-free survival. No matter with what drug you get to these lower values, you get a benefit in survival. But, as I mentioned, there is a much better probability that you'll get to these lower values if you receive treatment with dasatinib, nilotinib, or, bosutinib than if you receive treatment with imatinib as your initial therapy.



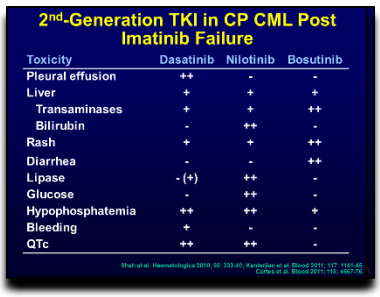
Slide 35 - Early Response to TKI: 3 Months or 6 Months?

Now, we don't know if at 3 months if a patient is falling behind with imatinib you should change. Some patients can catch up and by 6 months they've already reached that value of 10%. And those patients seem to still have a very good long-term outcome.

The patients who still fall behind, there's still less than 10%, they have a worse prognosis. Still, a good number of them will do well over time. But certainly you're starting to see fewer patients that don't do well.

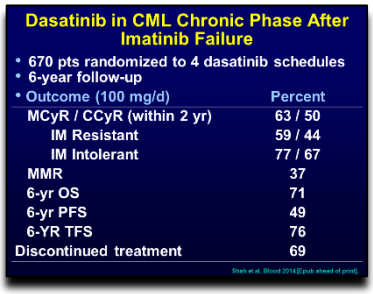
So, the conclusion is that we don't know that you necessarily have to change therapy at 3 months, but you really need to be very vigilant of those patients. And more important, you need to try to avoid patients falling into these lower responses.

[5] OS: Overall survival. EFS: Event-free survival



Slide 36 - Effect of Reduced Dosing on 3 Month PCR by Total Dose and Number of Missed Days

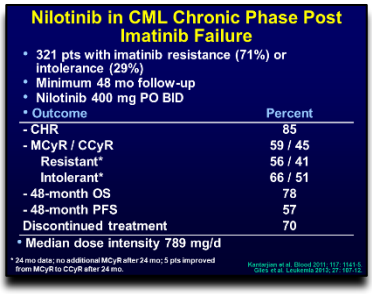
How do you do that? Well part of that is the drug, and part of that is, we've recognized that patients that take less than 80% of their prescribed dose, for example, that they miss more than 14 days during the first 3 months, they have a much lower probability of getting to these better responses. So, it is very important not to unnecessarily decrease the doses, not to miss any doses, etc.



Slide 37 - Dasatinib in CML Chronic Phase After Imatinib Failure

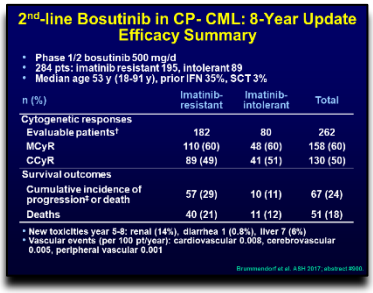
Now let me talk about what happens when the patients have received one therapy and that didn't work and you go to the next treatment. We have used the initial indication for the second generation TKIs, whereas for patients who had received imatinib and did not respond, so this is the data with dasatinib after imatinib failure.

And, as you can see, the results are very good. About 50% of patients achieve complete cytogenetic response. Many of them actually achieve a major molecular response. And the survival is actually very good, considering that these patients had already experienced failure to their initial therapy.



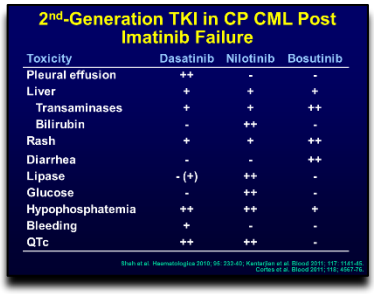
Slide 38 - Nilotinib in CML Chronic Phase Post Imatinib Failure

The same can be said for nilotinib, again this, was the initial indication after imatinib failure. And similar levels of response and similar overall survival.



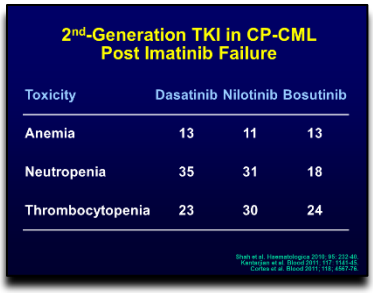
Slide 39 - 2nd-line Bosutinib in CP-CML: 8-Year Update Efficacy Summary

And finally, for bosutinib, again, the same, level of response. So all these 3 options are very good for patients who have received imatinib and experienced failure.



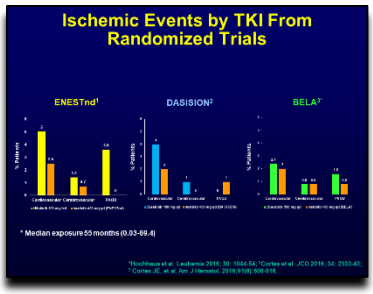
Slide 40 - 2nd-Generation TKI in CP-CML Post Imatinib Failure

I also want to highlight that all these drugs are safe, very well-tolerated, but they all have potential adverse events, that is important to recognize. The toxicity profile is a little bit different from one drug to the other. Dasatinib, for example, has more pleural effusion than the other drugs. Nilotinib has more hyperglycemia and hyperbilirubinemia. Bosutinib has more diarrhea and elevation of liver function tests. So, you just need to monitor your patients carefully and manage these adverse events.



Slide 41 - 2nd-Generation TKI in CP-CML Post Imatinib Failure

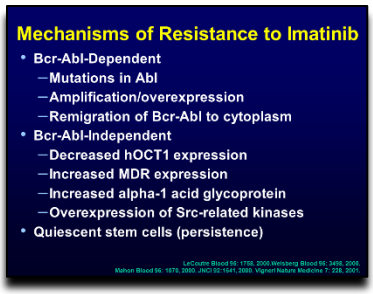
All of these drugs have the potential for myelosuppression, for causing neutropenia or thrombocytopenia or anemia. So also, very important to monitor the patients closely. Usually by 2 to 3 months these effects are gone, and the frequency of monitoring can decrease significantly. But particularly at the beginning, you need to monitor the patients carefully.



Slide 42 - Ischemic Events by TKI From Randomized Trials

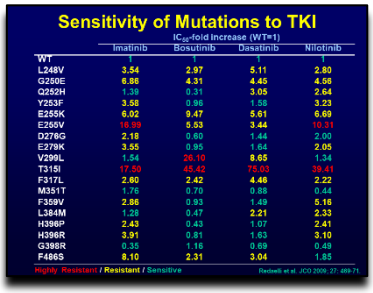
And we have recently come to recognize that, at least compared to imatinib, nilotinib and dasatinib for sure, and probably not so much bosutinib, they have an increased risk of arterial thrombotic events, cardiovascular, things like myocardial infarctions and angina. Also, cerebrovascular, like strokes and TIAs. And probably peripheral arterial disease as well.

So, this is important to recognize. This mostly occurs in patients that have other predisposing factors for these events, and it is very important to manage those other predisposing factors like diabetes and hypertension and hypercholesterolemia to minimize a risk of these patients.



Slide 43 - Mechanisms of Resistance to Imatinib

We know that the reason patients sometimes don't respond well to therapy is because they develop other abnormalities, most frequently mutations in the ABL-kinase domain.

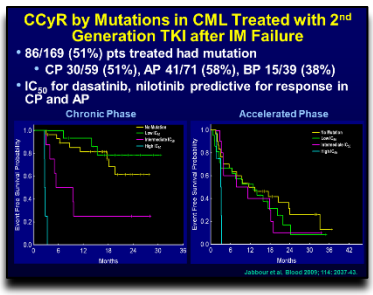


Slide 44 - Sensitivity of Mutations to TKI

And that means a change in the sequence that makes now the BCR-ABL not be inhibited by these drugs.

There are many mutations, more than 100 that have been recognized, but in this graphic, you see the most common ones and how the sensitivity to the different mutations varies from one drug to another. So, it is important, once a patient experiences resistance that you assess the mutations because that can help you determine which drug might be better to use next.

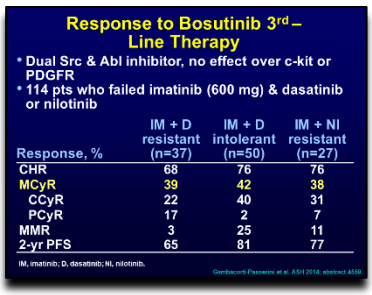
Now, in some instances there's no mutations. Half of the patients don't have mutations. In others, the mutation may respond equally well or equally poorly to the other inhibitors. For example, T315I is a mutation that did not respond to any of the drugs that I have discussed so far.



Slide 45 - CCyR by Mutations in CML Treated with 2nd- Generation TKI After IM Failure[6]

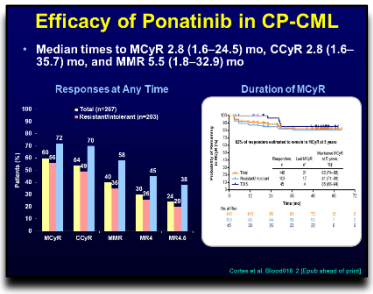
And when you select the drug based on the predicted sensitivity, you can expect a better outcome than if you treat patients with a drug that is not predicted to work against these mutations. And you can see that in the graphics here.

[6] CCyR: Complete cytogenetic response. TKI: Tyrosine kinase inhibitor. IM: imatinib mesylate



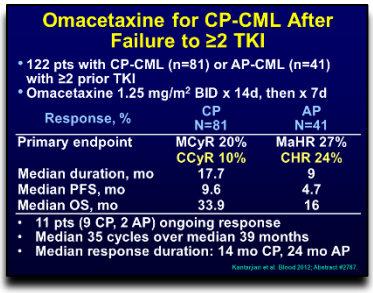
Slide 46 - Response to Bosutinib 3rd-Line Therapy

Finally, I'm going to talk a little bit about third-line therapy. Now the patient has received two TKIs. That is not as common, fortunately, but we do have such patients. Bosutinib has been prospectively investigated in that setting, and you see that about 40% of patients achieve a major cytogenetic response if they have received imatinib and dasatinib or nilotinib. So, it is a good treatment option for these patients.



Slide 47 - Efficacy of Ponatinib in CP-CML

But, of course, we also have ponatinib, a third-generation TKI, where these rates of responses are actually up to 60%, in all patients. And, very important, this drug is the only one that we have available today that works against the T315I mutation. And whether you have this mutation or not, you can respond well, and these responses are durable.



Slide 48 - Omacetaxine for CP-CML After Failure to ≥2 TKI

Finally, another drug that is approved in the United States, it's not a tyrosine kinase inhibitor. It's called omacetaxine. This is administered self-cutaneous. The main problem is myelosuppression.[7] It has more modest activity, but it can work in some patients, so it is something to consider for patients who have not responded well to any of the tyrosine kinase inhibitors.

Slide 49 - Optimizing Frontline CML Therapy in 2018

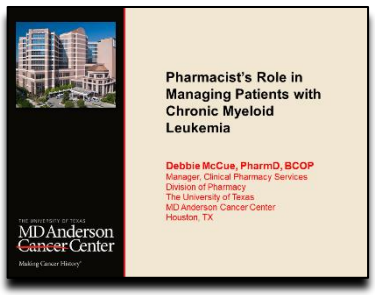
So, in conclusion, I think we have excellent therapy for CML today, where most patients can expect a normal life expectancy. But one important thing that we need to recognize is that the patient has to be managed holistically. It is not just checking their PCR and giving them the TKI. We need to manage their comorbidities or adverse events. All of that to try to provide to the patient the best long-term outcome possible.

We still need clinical trials to understand better treatment discontinuation and treatment in the advanced stages and all of that. So, I think this is a disease that still needs significant expertise, significant knowledge, and much research.

Slide 50 - Questions?

So, with this I conclude, and I'll be happy to turn over the program to Debbie McCue.

[7] Myelosuppression: A condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets.



Slide 51 - Pharmacist's Role in Managing Patients with Chronic Myeloid Leukemia

Debbie McCue, PharmD, BCOP: Hello, thank you for participating in this educational program. I will be discussing the role of the pharmacist in the management of patients diagnosed with chronic myeloid leukemia.

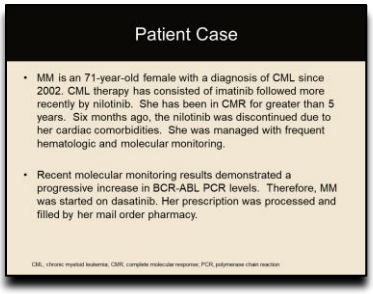
Slide 52 - Pharmacist's Role

Oral therapies can have a number of benefits. Patients enjoy the convenience of having therapy. They can self-administer versus the need to receive care in the hospital setting or clinic setting. So, they may require fewer healthcare visits, so the patients' day-to-day life may be less impacted. They can continue to work, for example.

But despite these benefits, there are a number of challenges with oral cancer therapies as well. It's much more difficult to confirm adherence to oral therapies versus medications you can document administration in the clinic or hospital setting. And then, also, with fewer healthcare visits, there are fewer opportunities to monitor patients on oral cancer therapies.

So, given these benefits and limitations, I plan to talk about the main areas that a pharmacist can be involved in care of these patients.

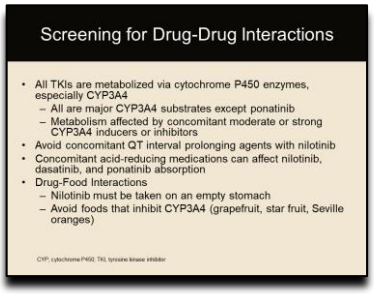
First, we're going to talk about screening for drug-drug and drug-disease interactions. We'll talk about assisting patients with access to medications. We'll talk about patient and caregiver education, and lastly, we'll talk a little bit about how pharmacists can otherwise serve as a resource to providers and patients.



Slide 53 - Patient Case

First, I want to start off with a patient case. This is MM. She's a 71-year-old female with a long history of CML, since 2002. Her therapy has consisted of imatinib, and most recently she was on nilotinib. She has been in CMR for more than 5 years. So, 6 months prior, the nilotinib was discontinued due to her cardiac comorbidities and she was being managed with frequent hematologic and molecular monitoring.

Recent molecular monitoring, however, demonstrated that there has been a progressive increase in her BCR-ABL PCR levels, and, therefore, MM was started on dasatinib. Her prescription was processed and filled by her mail order pharmacy.



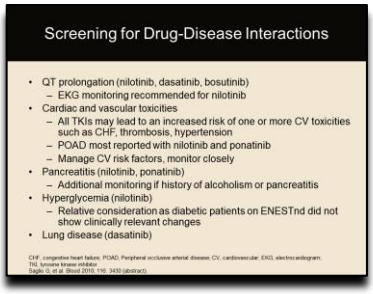
Slide 54 - Screening for Drug-Drug Interactions

So, for any drug therapy, it's important to consider interactions a new drug may have with a patient's other medications, diet, or comorbidities. All the TKIs are metabolized via the cytochrome P450 enzyme system. In particular, most are major substrates of CYP3A4, which can be affected by a number of common medications that are considered to be moderate or strong inhibitors or inducers with CYP3A4.

Medications that prolong the QT interval may also need to be avoided with some of the TKIs such as nilotinib, which has a boxed warning for QT prolongation. Acid-reducing medications are commonly used medications in the general population, and pharmacists and providers need to be aware that acid suppression can negatively impact the absorption of certain TKIs such as nilotinib, dasatinib, and ponatinib.

Further, nilotinib has very specific recommendations about taking on an empty stomach to avoid excess absorption, which would increase the risk of adverse effects, whereas other TKIs, such as bosutinib, may be best taken with food to minimize the GI toxicity.

Speaking about interactions, it's also important to remove food items that inhibit CYP3A4 activity in the gut, such as grapefruit, star fruit, Seville oranges, as these foods may increase absorption of the TKIs.



Slide 55 - Screening for Drug-Disease Interactions

In addition to reviewing the patient's concomitant medications for possible interactions, it's also important to review the patient's comorbid conditions to see if there are any interactions there.

This is just a list of examples. There may be other patient conditions or overlapping age and toxicities that may require a management plan.

As previously mentioned, some of the TKIs, and nilotinib in particular, have the risk of QT prolongation. So, patients with a known history of long QT syndrome or with concomitant QT prolonging medications may need further consideration and additional monitoring.

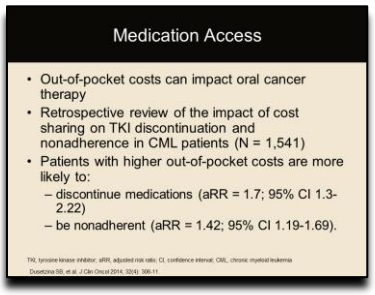
As Dr. Cortes mentioned, as we're gaining more experience with these agents, long-term toxicities such as cardiovascular toxicities may have come to light. All these agents in this class may be associated with higher risk of one or more cardiovascular toxicities such as CHF, thrombotic events, or hypertension, just to name a few.

Nilotinib and ponatinib are specifically associated with the risk of peripheral arterial occlusive disease. As patients may be on these agents for life, it's important for pharmacists and providers to assist patients in managing their cardiovascular risk factors, in order to minimize these risks. They should be educated on the importance of maintaining a healthy diet and weight, the need for exercise, and the need to control other conditions such as hypertension, diabetes, and dyslipidemia, which may impact their cardiovascular risk. Providers should also plan to monitor patients closely for these conditions as patients continue to age while taking TKI therapy.

Other conditions that may alter TKI selection or monitoring include the risk of pancreatitis seen with nilotinib and ponatinib, which may impact patients with a history of alcoholism or pancreatitis. Nilotinib has also been associated with hyperglycemia. However, a review of diabetic patients on the frontline nilotinib study did not show any clinically relevant changes in parameters such as hemoglobin A1C. So, this may be one association that may be managed with just some additional awareness and monitoring by the providers.

And then, as an additional example, patients with underlying lung disease, such as COPD, may not be the best candidate for dasatinib due to the risk of pulmonary arterial hypertension and pleural effusions, provided the patient has other TK options.

There were a number of examples on this slide and the previous. It's an important caveat that patients may be on TKI therapy for life. And reviews of concomitant medications and comorbidities should be an ongoing part of the patient's regular assessment by the pharmacist and provider as these items may change over time.



Slide 56 - Medication Access

Moving on to medication access. Targeted oral cancer therapies are unique clinical entities, and the costs of research and development of these new medications is significant and that cost is often reflected in the price.

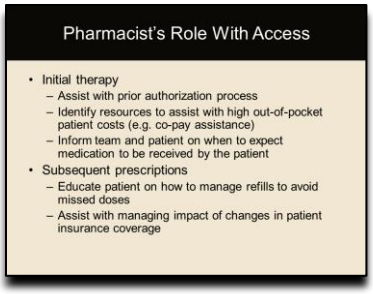
So, since oral cancer therapies frequently fall under the prescription benefit of one's insurance, the patient's out-of-pocket costs can be difficult to predict, significant, and can then impact outcomes.

As one example, there is a retrospective review of insurance claims, including prescription fills and cost-sharing information on just over 1,500 CML patients who were treated with imatinib or another TKI between 2002 and 2011. The authors looked at the primary outcomes of TKI discontinuation, non-adherence within 180 days of initiating imatinib therapy.

Discontinuation was defined as a break in therapy, i.e., lack of prescription fills, in this case that would result in more than 60 days without medication. Adherence in this study was defined as having a sufficient supply of the TKI to cover more than 80% of the days during the 180-day period after initiating the TKI therapy.

They looked at the copay amounts by the patient and the total monthly out-of-pocket expenses for the patient in the health plan. And the authors found, ultimately, that patients with a higher out-of-pocket costs are 70% more likely to discontinue the TKI and 42% more likely to be nonadherent to TKI therapy.

The authors also found that the mean monthly total expenditures has nearly doubled in that time frame, from 2002 to 2011. This trend, rising healthcare spending, I know has been a topic that's widely been discussed in recent years and does not appear to be reversing at this time.



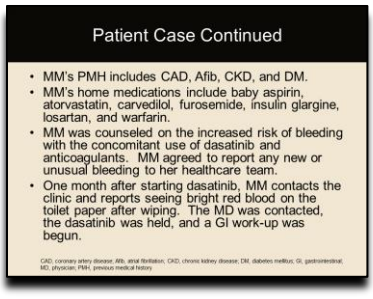
Slide 57 - Pharmacist's Role with Access

So, what's the pharmacist's role in medication access? Frequently these new prescriptions we'll not be able to fill on the same day, so while we're waiting for the prescription refill, we can help work on how to review in those drug-drug and drug-disease interactions, how we may have identified in coming up with management plans for those.

Those of us working in oncology clinics are frequently involved in the prior authorization process, including serving as like a contact person, assisting with documentation, providing those letters of appeal as necessary. Once the prescription has been processed, it's not uncommon to find out the copay is high and may be cost-prohibitive for the patient. So, we help point the patient to resources that assist with those out-of-pocket costs.

Pharmacists can also help the patient healthcare team stay informed of kind of the status of the prescription to mitigate any anxiety with any delays in filling the prescription. For subsequent prescriptions, we can work with the patient on how to manage refills to avoid missed doses. This includes utilizing the automatic refills, options that they may have with their pharmacies, or setting other reminders on how to receive their medications on time.

Patients will, obviously, be on these medications for years and insurance coverage may change over time, so it may be necessary to repeat some of these steps such as prior authorization or readdress out-of-pocket costs as the situation changes during the patient's course of therapy.

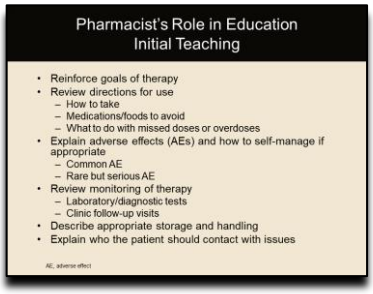


Slide 58 - Patient Case Continued

Now I'd like to go back to our case for just a moment and tell you a little bit more about MM. Her past medical history includes coronary artery disease, Afib, chronic kidney disease, and diabetes. Her home medications include a baby aspirin, atorvastatin, carvedilol, furosemide, insulin, losartan, warfarin.

Her medications and comorbidities reviewed, we noted that there was a moderate drug-drug interaction between her baby aspirin, warfarin, and the planned dasatinib, due to the risk of bleeding. So, at the time that MM was started on dasatinib, she was counseled on her increased risk of bleeding and agreed to report any new and unusual bleeding to her healthcare team.

Unfortunately, one month after starting the dasatinib, she contacted the clinic to report seeing bright red blood on the toilet paper after using the restroom. The oncologist was contacted, she was told to hold her dasatinib, and was brought to the clinic for workup of this presumed GI bleed.



Slide 59 - Pharmacist's Role in Education: Initial Teaching

As with any medication or patient population, the pharmacist can play an important role in educating the patient about their therapy. For the education of a patient starting on new oral cancer therapy, there are several areas the pharmacist should review with the patients.

First, it's important to reinforce the goals of therapy. These were already discussed by the oncologist; however, having clear goals are important, and patients that understand goals of therapy are more adherent to therapy.

Next, it's important for the patient to understand how to take the medication appropriately. Any medications or food that should not be taken at the same time should be discussed like we previously mentioned.

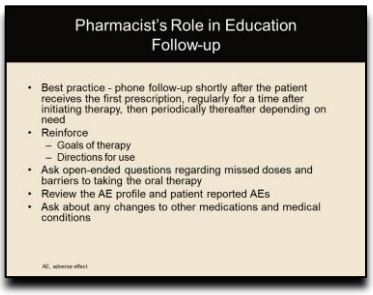
Lastly, we ought to talk about what to do in case of missed doses, or if the patient takes an extra dose. Adverse effects should be explained as well that need self-management by the patient. This includes common side effects as well as rare but serious side effects. My colleague Sue Kaled will speak to you shortly about the common side effects with the TKIs and how they are managed.

In the case of our patient, she was educated about her bleeding risk with dasatinib, and promptly contacted a clinic as she was instructed.

It's a good idea to also review the expected monitoring plans for these oral agents. Dr. Cortes already covered the usual monitoring schedule, and the patients that know how often they need to be seen, as well as what labs should be monitored, are better advocates for themselves, in the event of any missed appointments or changes in providers over time.

And, also, with any new medications, you should discuss with the patient storage and handling, provide a contact for who the patient should call with any issues.

And, finally, when doing any patient teaching, it's important to verify that the patient and caregiver understands what was discussed.



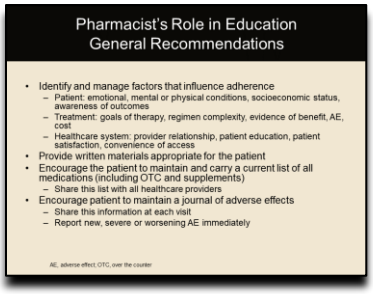
Slide 60 - Pharmacist's Role in Education: Follow-up

As we discussed earlier, the few challenges with oral cancer therapies are monitoring for adherence, and other issues. ASCO/ONS actually has standards for safe administration and management of oral chemotherapy, and they recommend having a process for assessing patient adherence. So, after the initial prescription is provided, a number of clinics meet this standard by providing a phone follow-up.

The purpose of the phone follow-up is to confirm the patient received the medication, which could be a question mark depending on the financial status of patients. Kind of re-review some of those initial education points that you may have discussed, identify any toxicities or problems that their patients are having so far.

It's important to kind of re-review on that phone follow-up, the directions for use and adverse effects and monitoring. At subsequent clinic visits you should also update the patient's medication list and medical history, in order to identify any new interactions with their TKI.

With any follow-up, it's important to ask open-ended questions to identify adherence issues. Have the patient tell you how they take the medication, specifically probing about timing and food effects as appropriate. Have the patients tell you how many doses they may have missed, rather than asking yes/no questions about if they missed any doses, and inquiring about any financial concerns which may be affecting their ability to fill their prescriptions.



Slide 61 - Pharmacist's Role in Education: General Recommendations

One of the most important things we can do as pharmacists during our interaction with these patients is to help identify and manage those factors that affect medication adherence. Generally, those factors can be grouped into 3 categories: patient factors, treatment factors, and health system factors.

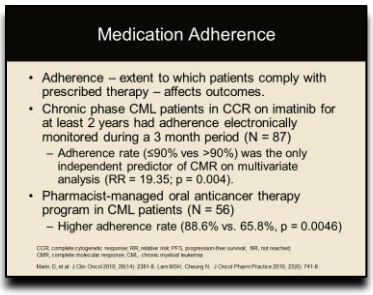
Examples of some of those factors are on the slide and we've already talked about several of them, such as awareness of expected outcomes, cost, and education.

Verbal education is obviously important, but it's also important to follow it up with some written documentation as well, as patients tend to recall only a portion of any initial teaching. That's why we recommend to review the key points during the subsequent phone calls and visits as well as providing that written documentation.

As these patients tend to be, kind of middle-aged adults, they tend to have comorbidities and may see other healthcare providers. So, we encourage patients to carry a list of all their medications, including any over-the-counter medications or supplements they may take, to share this list with all healthcare providers that they see. You should also encourage the patient to write down any potential adverse effects or other concerns they may have and bring this list to their clinic visits each time.

Some patients may benefit from maintaining a diary, a journal of side effects, to help the healthcare team interpret the information as far as frequency and persistence of toxicities.

Considering that these therapies are long-term and perhaps life-long in most patients, a persistent minor toxicity such as diarrhea or fatigue may be as much of a barrier to adherence as rare, uncommon side effects.

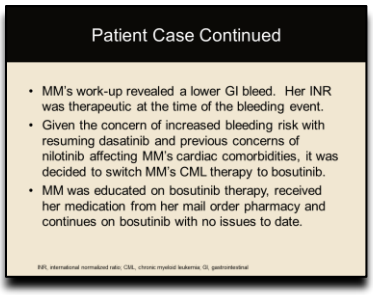


Slide 62 - Medication Adherence

So, we've been talking about adherence for a number of slides and why that is so important in these patients. The patient's ability to comply with prescribed therapy has been shown to affect outcomes. Dr. Cortes mentioned some of the data about missed doses or reduced doses in his presentation, the ability to achieve the anticipated response by certain milestones.

There is another paper that looked at the impact of adherence with TKIs and CML outcomes from that. They looked at a group of CML patients in complete cytogenetic response for at least 2 years. This group had their adherence to imatinib monitored using a microelectronic monitoring device that was in the cap of their prescription bottle for a 3-month period during that time. The primary outcome was molecular response, and they found that the only independent predictor of complete molecular response was adherence using a cutoff of 90%—so being able to take in 90% of the expected doses during that time frame. No molecular responses were seen in patients with an adherence rate of less than 80% of doses.

There's also been a little bit of publication in the outcomes of pharmacist-managed oral cancer therapy programs in CML patients where both patients seen with the aid of a pharmacist had a higher adherence rate of 88.6% compared to usual care.



Slide 63 - Patient Case Continued

Now let's continue with our case. Unfortunately, MM's workup did reveal a lower GI bleed. Her INR was within normal therapeutic range at the time of the bleeding event. So, given the concurrent bleed concerns, we decided not to continue the dasatinib. So, recall that this patient had previously been on imatinib and nilotinib. So, fortunately, since we have several TKIs to choose from in the treatment of CML, MM was switched to bosutinib which she was educated on her bosutinib therapy, received her

medication from the pharmacy, and so far remains on therapy with no issues to date.

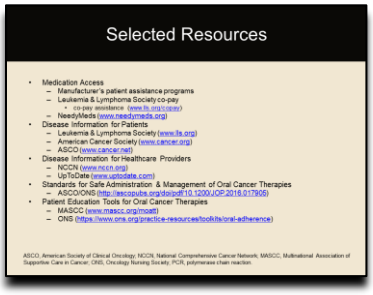
Slide 64 - Pharmacist's Role as an Information Resource

Pharmacists may find themselves in a position where they're not able to have that direct face-to-face interaction with a patient but may be supporting the patient in other ways. Some clinics or healthcare plans may establish programs or pharmacists provide those phone follow-ups that we talked about to ensure that the patient is adherent to the therapy and not experiencing any issues.

Pharmacists, regardless of setting, can also assist patients with overcoming adherence problems using a number of tools that are available, such as reminder tools, use of diaries and pillboxes, apps for helping with adherence.

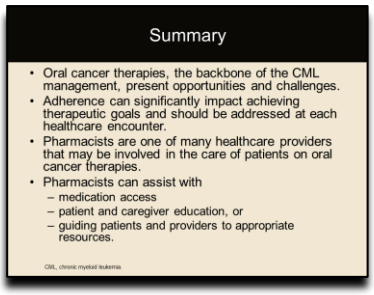
They can also impact a larger audience providing talks or leading discussions at local and national patient support groups. Pharmacists can also help other healthcare providers in the management of these patients, helping providers navigate the access issues or adherence barriers that we've discussed.

Pharmacists can help screen for those drug-drug and drug-disease interactions and make recommendations for monitoring plans, and they also assist the healthcare team in recognizing and managing those adverse effects that patients may experience over time.



Slide 65 - Selected Resources

Provided is a list of some of the resources that pharmacists and other providers can make use of when managing these CML patients.



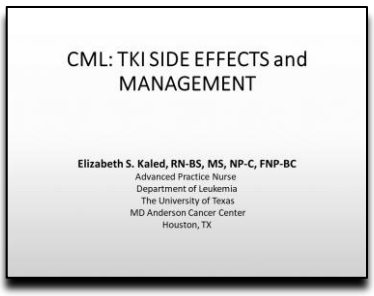
Slide 66 - Summary

In summary, oral cancer therapies are integral to the management of CML, which is now effectively a life-long therapy for most of these patients. Pharmacists and providers should recognize that long-term oral cancer therapy presents huge challenges. Adherence can significantly impact the achievement of our goals of therapy and should be assessed and addressed at each visit.

Pharmacists are just one of many healthcare providers that may be involved in the care of these patients and in a position to impact adherence.

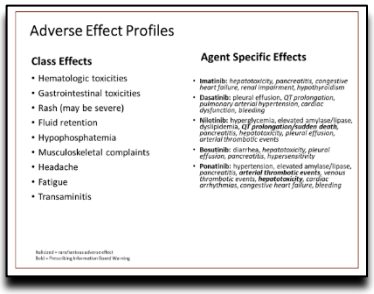
Pharmacists can also assist with medication access; provide education to patients, caregivers, and providers; and otherwise serve as a resource to all with the goal of improving CML patient outcomes.

And this concludes my part of the presentation. I'd now like to turn it over to Sue Kaled who will discuss the TKIs and toxicity management.



Slide 67 - CML: TKI Side Effects and Management

Elizabeth Susan Kaled, RN-BS, MS, NP-C, FNP-BC: Thank you for participating in this educational discussion about CML and the treatment with tyrosine kinase inhibitors. My name is Elizabeth Susan Kaled, and I work at MD Anderson. And I'm an advanced practice nurse.

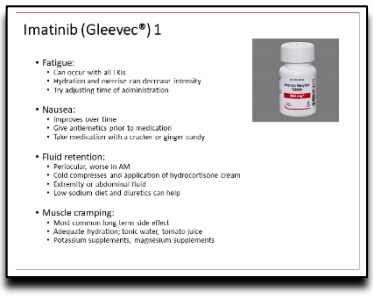


Slide 68 – Adverse Effect Profiles

I'd like to start off by, reviewing the adverse effects of TKIs. As a class effect, we have the hematological toxicities and GI toxicities. Rash, it ranges from, slight, could be severe on, with some of the TKIs slightly low phosphorous. Musculoskeletal complains, range from arthralgias or myalgias to actually cramping, common headache, fatigue, and transaminitis.

Then you have your agent-specific, effects. And some of them are more hazardous than others like imatinib, is really mainly irritative effects. We rarely have the hepatotoxicity or the pancreatitis. We do have a lot of GI complaints and a lot of the cramping.

Dasatinib it can be, major with the pleural effusion. It's a little bit less with the lower dose that we start off with now, the 50 milligrams per day. Your nilotinib does have the prolonged QT level and also a sudden death syndrome that we have to be aware of, and that's that black box warning. Bosutinib definitely has, diarrhea as a side effect, and we have to be aware of that. Ponatinib is saved for the specific T315I mutations for it does have arterial thrombotic effects and venous thrombotic effects.



Slide 69 - Imatinib (Gleevec®)-1[8]

The first drug I'm going to talk about is Gleevec® [(imatinib)], and this is the first one on the block that came out in 1999, first given to patients in 2000. It's used as a treatment for chronic phase CML. And some of the most common side effects that you're going to encounter are, one, the fatigue. And this is essentially across the board. We suggest trying to teach the patient to become quite hydrated, keep drinking water. It can be tea, juice, or any other fluids except alcohol, which we actually tend to ask them to avoid.

Also, we counsel them on how exercise can sometimes decrease the intensity of the fatigue. Occasionally, we tell them to play around with when they take the medication. We generally want them to take it at the same time every day. But there's times when you take it at night—then the fatigue hits at night and they can just sleep through one of these side effects without doing anything extra in their life.

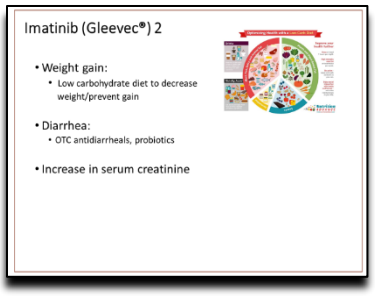
The next, problem, again, is nausea, and this also can be fairly much across the board. It also is helped with taking some hydration but in smaller amounts. You can use some antiemetics initially prior to taking the medication. Also, try taking it with just a slight bit of food in the stomach before taking the pill. This doesn't mean a huge meal but just some dry toast, cracker, or even ginger candy can help while you're taking the medication. The exception to this, as we'll come to, is with the nilotinib. We don't want anything in the stomach at that time. There is a time to eat before and a time after when you may not take anything by mouth except the pill.

Our next problem we can come up with is fluid retention. This is more prevalent in imatinib, as globally as it is, but first, we would see some periocular edema. It's normally worse in the mornings, and it can abate during the day. We ask them to try cold compresses and, at times, then application of Anusol-HC® [(hydrocortisone acetate in a hydrogenated vegetable oil base)] can help decrease the severity.

[8] In general, concomitant alcohol consumption with any of the TKIs would not be recommended. However, the occasional alcoholic beverage may not pose a problem in a clinically stable patient, as long as the consumption is occasional, not chronic, and not in excessive amounts on those occasions.

It can also have extremity and abdominal fluid retention. With that, there are diuretics that can help, or a low sodium diet can help with that also. Remember, when you're giving the diuretics, you do have to then monitor their potassium levels.

Pretty much all the patients that take imatinib can get some muscle cramping, the most common long-term side effect. Again, we were stressing adequate hydration. There can be some response to potassium or magnesium supplements. Some people use tonic water, tomato juice. Some people even use pickle juice. There are other strategies: I did have one patient that took a little packet of mustard every time she started getting these cramps. There's nothing universal, but to try these different things to ameliorate that side effect.

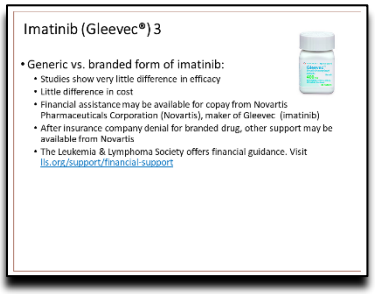


Slide 70 - Imatinib (Gleevec®)-2

Weight gain is a pretty serious side effect for some of the patients. It is not frequent, but people can definitely start to gain weight on the Gleevec® [(imatinib)] for many other reasons besides just the Gleevec® [(imatinib)] therapy. We suggest a low carbohydrate diet, Sugar Busters, if you want to name one or the South Beach Diet are good. And there's a lot of information about that that can be obtained, either in the Internet or from your dietitian that will work closely with you in any of the oncology settings.

Diarrhea may occur, and we do use probiotics or over-the-counter antidiarrheals. And this is also easing off after they've been on it for a few months.

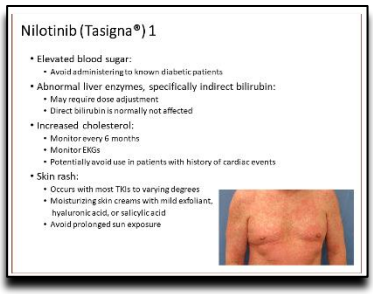
Another side effect that we have, but it occurs later with this tyrosine kinase inhibitor (remember, we have had some people on this medication for about 20 years since its inception) and we can see the creatinine start to rise. But, also notice that the people are also 20 years older at this point, so it could be just a part of aging with the additional comorbidities, the hypertension that may have occurred along the way. But it's something to watch for.



Slide 71 - Imatinib (Gleevec®)-3

Another thing we'll discuss here then is, also, the current discussion between generic and brand form of imatinib. There have been studies, especially in Europe, that are showing that there's very little difference between the efficacy of either medication[9]. There may be a difference in side effect profile that people either perceive, or their's is actual, but it's actual for them. Unfortunately, there is very little difference in the cost, at least in the United States, between these medications.

So, if we are trying to get assistance if they can't afford them, we usually go straight to the Novartis company. The brand must be ordered, then denied by the insurance company. Then you can apply for the assistance. So, it's a few more steps, but that is one way we can try and get some people back on the brand if they are thinking that this is best for them.



Slide 72 - Nilotinib (Tasigna®)-1

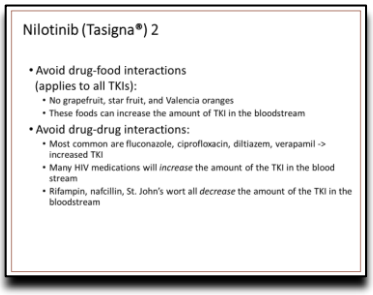
I'm going to move on to nilotinib, which is used for chronic or accelerated phase of the CML. Some things to consider before starting this are, one, if they have ever had any cardiac issues or if they are diabetic, that you may want to avoid this medication and go onto a different TKI. But, when you do start it, then we should be looking for any kind of an elevated blood sugar. We also have to be monitoring closely for any abnormal liver enzymes.

These definitely have a rise in the indirect bilirubin. So, you don't want to stop your drug for mild rises in this—you keep going. Many times the direct bilirubin is not affected, but that is something you want to keep monitoring for, especially in the first year to 2 years of therapy.

[9] Kozaric, Amina Kurtovic et al "The Comparison of Efficacy Between Generic and Branded Imatinib in Achievement of Overall Survival and Cytogenetic Responses in CML Patients in Bosnia and Herzegovina." Blood128.22 (2016): 5451. Web. 28 Nov. 2018.

Any increase in the cholesterol, you're again monitoring this at least every 6 months, monitoring EKGs. And you will also want to avoid this in any other patients with a history of cardiac events if they're on, say amiodarone, that's going to have a drug-drug interaction here. It is excellently described with Debbie's discussion. So, watch out for any of these things and discuss it clearly with the pharmacist for they have more expertise in this area.

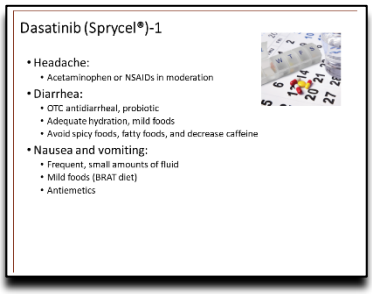
Another thing that is pretty much concurrent with all the TKIs is a skin rash can form in varying degrees. But we do suggest using moisturizers and skin cream. It can be with a mild exfoliant, hyaluronic acid or salicylic acid can help with the moisturizers to decrease this effect. We also emphasize to avoid any prolonged sun exposure.



Slide 73 - Nilotinib (Tasigna®)-2

We're asking you to monitor for any kind of drug-drug and food-drug interactions with this medication. And this is just some further information that would go along with Debbie's discussion.

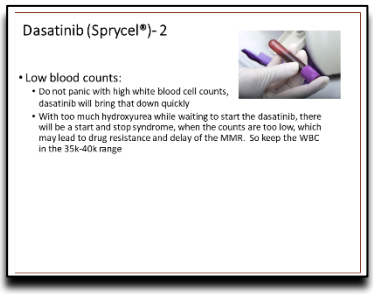
Oh, and I do want you to remember to monitor for any amylase and lipase elevations forming. Nilotinib may have occurrences of pancreatitis.



Slide 74 - Dasatinib (Sprycel®)-1

Moving onto dasatinib. It has a common side effect of headaches. We do suggest just occasional Tylenol®-[(acetaminophen)] or NSAIDs but in moderation, not every 4 hours. We want like once, twice a day max, just to see if that does help. And it is one of those that can be easing off over time if you just get them through the first few months.

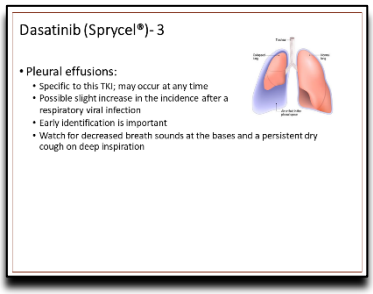
Again, diarrhea can be occurring with this, nausea and vomiting.



Slide 75 - Dasatinib (Sprycel®)-2

And the low counts can be across the board but are more common with the dasatinib and nilotinib. But I do want to state that prior to starting either of these medications, we don't want to bring down the high white count so quickly or down too low, for these drugs will also decrease the counts. So, we don't want prior to starting with treatment, down to a white count say of 5 or 6.

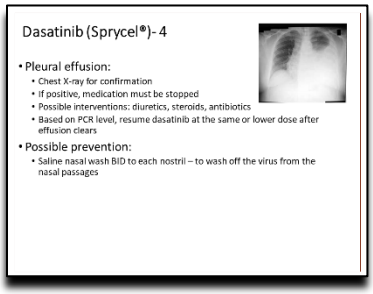
Go ahead and start them in the 30- to 40,000 range, for this drug will bring it down. And this may lead to decreasing the start and stop that we're having in the first few months, because we want to keep a consistent drug going, to help increase the rate and to the achievement of an MMR.



Slide 76- Dasatinib (Sprycel®)-3

Dasatinib is specific for its type of fluid retention. This would be pleural effusions. I do want to say that this can occur pretty much at any time during the course of this medication. I've noticed a slight increase after some respiratory viral infections, but this does not necessarily have to be the case. They can get it out of nowhere also.

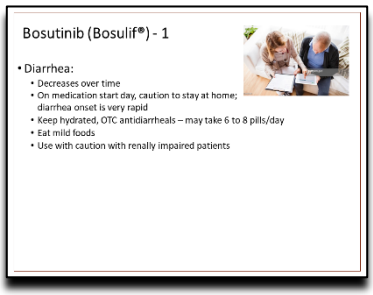
If this does occur, sometimes you pick it up on your physical exam. So, when they're coming in for their bloodwork, physical exam, obviously, with each visit is imperative. You can pick up decreased breath sounds at the bases. While you're making them take a deep breath, they might have this dry cough.



Slide 77 - Dasatinib (Sprycel®)-4

And that would trigger me to get a chest x-ray and make sure that they don't have the development of any kind of pleural effusions. With this, depending on the degree of the pleural effusion, you may stop the medication, or you may not. Preferably, we'd like to go through it, see if diuretics can help. At times we select to use steroids or antibiotics. But, and depending on the PCR level, you may resume the dasatinib at the same or lower level, depending on the preference of, obviously, your oncologist and the degree and length of their MMR.

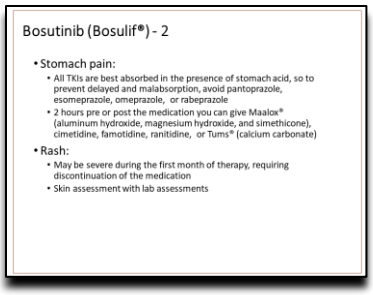
Possible prevention for this could be telling them during the cold and flu season to use saline nasal wash twice daily. This can help clear the virus from the nasal passages and may decrease the severity or possibly prevent the infection from the virus that may lead to this.



Slide 78 - Bosutinib (Bosulif®)-1

With bosutinib, it has many of the same prior side effects. But this one definitely, you have a side effect of diarrhea. This is a much, most common with this and, also, can occur on exactly the same day that you start the medication. So please tell your patient to be around home when you start this medication on course one, day one. And when it occurs, it can be a very rapid onset for this. We want the patients to be hydrated. They can use OTC antidiarrheals. And you can take up to 6 to 8 pills of those a day but not every day, just start for the first few days, and then go back down to the recommended doses.

Because of the potential degree of diarrhea, we use any caution with any patient with renal impairment for this medication. Close monitoring within the first few weeks of this would be very imperative if they are having frequent diarrheal stools of 6 to 8 a day. You do need to be in close monitoring with your patient and phone follow-up is suggested.

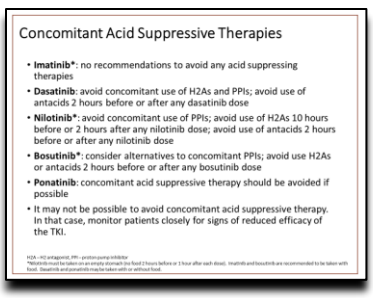


Side 79 - Bosutinib (Bosulif®)-2

With all the TKIs, you may have some stomach pain. This may occur because we do ask them to avoid taking any of these following medications: your omeprazole or pantoprazole, at least for the duration of this therapy for it could decrease absorption of your TKI.

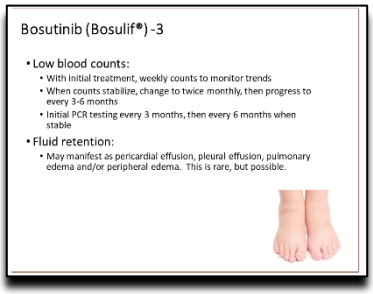
You can take two hours pre or post the following medications: the Maalox® [(aluminum hydroxide, magnesium hydroxide, and simethicone)], cimetidine, famotidine, ranitidine, or Tums® [(calcium carbonate)] to help decrease stomach pain with that or with all. But the nilotinib, you can try taking some dry toast or some crackers to help decrease any kind of abdominal pain with your medication.

Rash, as with other TKIs, but I have noted that sometimes this one is very severe with bosutinib, and we have had to take some patients off the medication because of this. So please be aware that this may require admission in the hospital if it is severe because it could be over their whole body. And just keep close monitoring of your patients.



Slide 80 – Concomitant Acid Suppressive Therapies

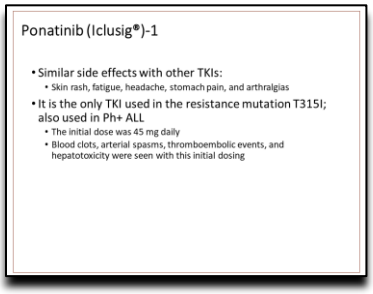
With all the TKIs, we do suggest that we don't take any of the PPIs for it can reduce their absorption in a non, acid environment. There's a little less of that problem with the imatinib, but all your second-generation and third-generation TKIs do have this problem.



Slide 81 - Bosutinib (Bosulif®)-3

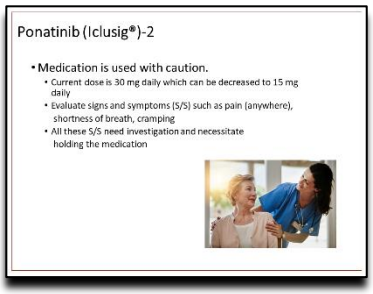
Next, low blood counts, as I discussed with the dasatinib. You do want to monitor (even when the counts are stabilized), you do want to slowly progress and decrease the number of times you monitor the counts. But, really, every 3 to 6 months would be very good for patients on the long term with these medications.

And here with the bosutinib, the fluid retention can manifest either as a pericardial effusion, a pleural effusion or pulmonary edema, and peripheral edema. It's rare but possible, so keep monitoring for these kinds of problems.



Slide 82 - Ponatinib (Iclusig®)-1

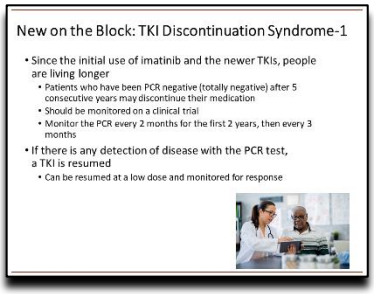
The last one we'll talk about is the ponatinib, the Iclusig®. This one we only use in blast phase or T315I mutation setting. It does have similar side effects with other TKIs—the skin rash, fatigue, headaches, stomach pain, and arthralgia—but the initial dose we used in the initial studies was 45 milligrams daily, and we did have, unfortunately, the occurrence of blood clots, arterial spasms, thromboembolic events, and some hepatotoxicity.



Slide 83 - Ponatinib (Iclusig®)-2

So, this drug was held for a while and we couldn't use it. But because of the effectiveness in the T315I and also in the blast phase, it was reinitiated at a dose of 30 milligrams daily. But with your oncologist, obviously, it can be adjusted down to 15 milligrams or only daily. But we first want to get a nice, deep molecular response, and then we can move it down. But any signs or symptoms of any kinds of the above side effects, definitely any kind of cramping, shortness of breath, all need to be investigated immediately. Not at the next clinic visit but definitely immediately. And you may hold that medication until you get that thoroughly evaluated.

And of note, we also use this with Philadelphia chromosome-positive ALL, and the same cautions and restrictions apply. You have to get very close. Side effects have them, and very close contact for any kind of side effects of shortness of breath, pain on inspiration, or anything of that nature.



Slide 84 - New on the Block: TKI Discontinuation Syndrome-1

And this is all I have to talk about at this time with the side effects, but I do want to now mention that what was alluded to was the discontinuation of the medications. This is something that may occur, but, of course, we're finding things happening after we discontinue the medication.

And as I show on the slide, that we are treating a leukemia, we are treating a cancer, and this is a miraculous and fantastic event that has occurred, and I'm very happy to have seen it in my lifetime, to not see people die of CML at the frequency that we did prior to 2000. As I stated, some of our patients we've been monitoring for 20 years.

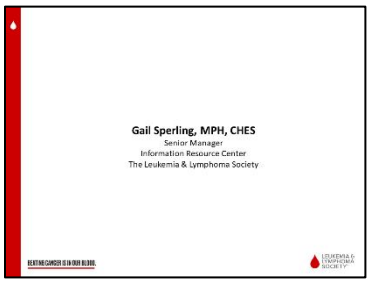
After our physicians have clearly evaluated this, they are letting people stop their medication after 5 years of continuous PCR-negativity. But we do want to say that they are being discontinued and they are being monitored on a clinical trial. And maybe, we just take their names down, and we keep a close monitoring of them.

For the discontinuation of the TKIs after you've been PCR negative, we do suggest that every two months you do get a PCR drawn. You go to the same lab that you've been having it drawn so that there's consistency. The reason for the close observation is that there is a chance that you will have a recurrence of the disease, and at the earliest time possible, it's much easier to get, you back into a

good PCR negativity and, therefore, being able to continue your life without a change in any of the TKIs to a stronger or a different formulation.

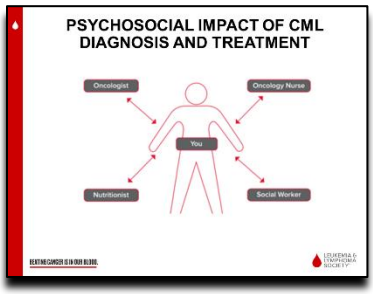
If there is any detection of the disease, we definitely resume the TKI. And at that time, it could be at a lower dose. And then we do monitor, again, back to the every 2 to 3 months for disease response.

I thank you very much for your time and hope this was very informative for you.



Slide 85 – Title Slide

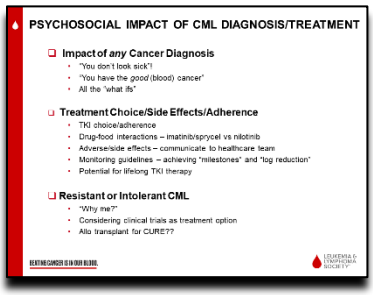
Lauren Berger: Thank you Dr. Cortes, Dr. McCue, and Nurse Practitioner Kaled, for your very clear and informative presentations. I am now pleased to turn the program over to Gail Sperling.



Slide 86 – Psychosocial impact of CML Diagnosis and Treatment

Gail Sperling: Thank you, Lauren. I'm Gail Sperling, and it's really my pleasure today to share some key issues of concern to chronic myeloid leukemia patients, family members, and caregivers.

As Dr. Cortez mentioned earlier in this program that one of the biggest cancer achievements, especially over the past 20 years, has been the management of CML; and I feel that both Dr. Cortez and Dr. McCue did such an excellent job discussing treatment, side effects, drug interactions, treatment adherence, and other factors associated with that. But even with these amazing advances, there are still a variety of issues that need to be addressed and communication that needs to happen between the patient, the family, and the healthcare team.



Slide 87 – Psychosocial Impact of CML Diagnosis/Treatment

So I plan to talk today about some of the psychosocial issues that can arise when a loved one has received a diagnosis of CML and how important the social worker and other members of the healthcare team are in providing support, guidance, and resources throughout the cancer journey. So in some cases you'll note that I'm actually using quotes from patients.

So let's start with the impact of a cancer diagnosis. We frequently refer to this as "deer in the headlights time," when patients and families are saying, "What?, How?, this is impossible." With a diagnosis and beginning of treatment, some CML patients may hear, "Oh, you have the good cancer" or "you don't look sick," although many patients may look unwell. And even once they've obtained good information and understand that there are currently great treatment options, there are still a lot of what I call what-ifs. What if it doesn't work for me? What if I always have these side effects? What if I have to take this medication for life? What if I want children? Again, many, many what-ifs.

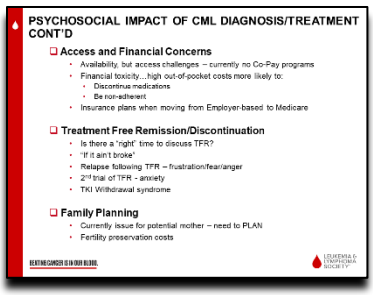
Well, treatment choice and side effects and adherence have already been addressed today; and we know that research shows that compliance with a prescribed treatment can affect the outcome and the ultimate goal of achieving those anticipated responses by certain milestones. And since it's a pretty complicated decision, it's vitally important to encourage open communication with the healthcare team throughout so that the treatment they choose ultimately fits into the patient's normal routine in the best possible ways. They need to consider the drug-food interactions, and the patient and his or her family need to let that treatment team know if there are any side effects or any problems that make it challenging for them to take the meds exactly as prescribed.

Equally important are the treatment milestones and monitoring by PCR. Waiting for these results and interpreting them can be a time of stress for the patient, especially when this is done so regularly in the

first 18 months. What does it mean to the patient and family if they haven't quote/unquote "achieved those milestones" and understanding terms like log reduction?
Dr. McCue brought up that CML patients may need to be on TKI therapy for life. She discussed the advantages of oral therapy but also the challenges. So this can require patients to really wrap their head around the good possibility of lifetime therapy, and that is something that will always need to be considered as the patient ages and finds him or herself on other medications and experiencing comorbidities.

So although a lot of progress has been made in treating CML, not all CML responds well to treatment or a treatment may work at first but then becomes less effective. Or maybe there are intolerable side effects. A common response to this can be, "Why me? The pills work for everyone else." So a bit here about resistant or intolerant CML.

Stem cell transplant is rarely used as a frontline therapy, but it's important to recognize that it's still a treatment option for some patients who are first diagnosed in or progress to some of the advanced phases of CML. It's still a valued option for patients who have received several TKIs without the desired response. An allo stem cell transplant can be curative in some patients, but it's not without challenges; and this can be a complicated decision as well.



Slide 88 – Psychosocial impact of CML Diagnosis/Treatment Cont'd
We definitely have to address access and financial concerns. Oral cancer therapies frequently fall under the prescription benefit of one's insurance, and the patient's out-of-pocket costs can be difficult to predict.

Compliance is a huge issue, especially for younger patients taking TKIs. Dr. McCue and the authors found ultimately that patients with higher out-of-pocket costs are more likely to discontinue the TKI and more likely to be nonadherent to therapy.

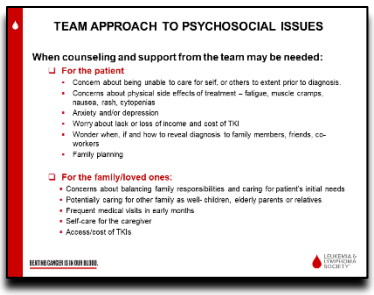
It's really important to know and plan for this. There are some financial assistance programs, but currently I'm not aware of any programs that help with copays for patients with CML.
Another area of concern are those patients who are currently insured through their employer and looking at Medicare. It's important to really explore insurance options at this phase of life and be sure that all the treatment options are part of insurance formularies.

Let's talk a bit more about treatment-free remission (TFR) and discontinuation, even though it's been pretty thoroughly presented today. It's still a hot topic among patients. Is there a right time to discuss it? Surprisingly, or maybe not so surprisingly, patients who are tolerating the treatment well and have good quality of life, may or may not be interested in TFR. For many the philosophy can be "if it ain't broke."

Given that currently right around 50% are relapsing following TFR, we still hear about a lot of frustration, fear, anger, and for some, "Well, when can I try it again?" And for some that are successful at treatment-free remission, there may be TKI withdrawal syndrome to manage.

According to current data, the best outcomes for pregnancy in CML patients occur when patients and their team actually plan for a pregnancy and develop a treatment strategy, including careful monitoring.

Currently, there's no data to suggest that any TKI can be taken safely during pregnancy, so potential parents need to receive counseling and understand current recommendations.
Fertility preservation costs may be a concern as well, and there are several organizations that address this and it can be a great and important resource.



Slide 89 – Team Approach to Psychosocial Issues:

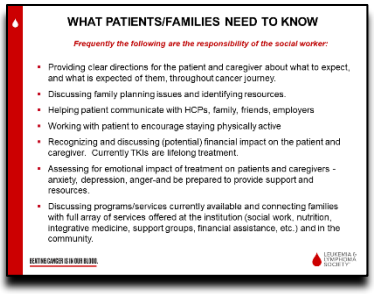
So we now understand that for the majority of CML patients diagnosed today, they can expect to have a near normal life expectancy and especially those that have a good response to therapy. That means that a patient that has CML, that's properly managed, and that has good access to treatment, a key point being good access, is likely to live as long as other individuals of the same age and sex, and they're not going to die of leukemia.

But in addition to the previously mentioned areas, there are some key times when counseling and support from the oncology team may be needed. There may be concerns about being able to care for him or herself or others to the extent they were able to prior to diagnosis. This may be especially true in the early weeks and months following diagnosis.

Patients may also struggle with the physical side effects of treatment. Some patients may experience anxiety and/or depression. This can be especially true in patients who are already predisposed to one or both. And there may be worry about lack of income and the cost of TKI.

Many patients may wonder when, if, and how to reveal their CML diagnosis to family members, friends, or coworkers. This can be a very personal decision, and as previously mentioned, we can't forget the issue of family planning.

For the family loved ones, there can be some of these same concerns – balancing work, family responsibilities, and caring for patients' initial needs. Potentially caring for other family as well, children, elderly parents or relatives, the need for frequent medical visits, especially in the early months, self-care for the caregiver, and, again, concerns about access and continuing to cover the cost of TKIs.

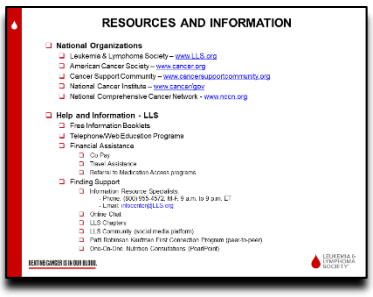


Slide 90 – What Patients/Families Need to Know

So, depending on the institution or practice, helping patients and families identify what they need to know and do to cope with a CML diagnosis and treatment is the responsibility of the social worker. Frequently this can be the responsibility of other healthcare providers, including physicians assistants, nurse practitioners, and patient navigators. These healthcare providers can assist with encouraging open communication about what to expect throughout the cancer journey, provide referrals to appropriate community organizations, encourage the patient to stay physically active, discuss any financial issues that may impact taking TKIs as prescribed, and assess for the emotional impact of diagnosis and treatment in both the patient and his or her family. In other words, be the quote/unquote "go-to person" for the many issues that impact patients and caregivers.

Slide 91 – Current and Relevant Information

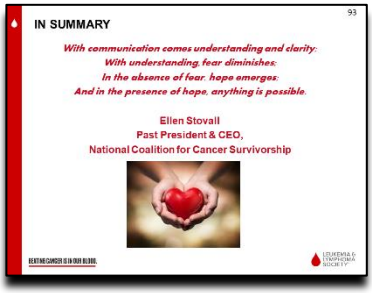
A variety of CML-specific and psychosocial materials are available through The Leukemia & Lymphoma Society. I've provided some examples here, including both the guide and the comprehensive booklet as well as some of the support information. All of these materials are available at www.lls.org/booklets.



Slide 92 – Resources and Information

There are a variety of national organizations, including The Leukemia & Lymphoma Society, The American Cancer Society, Cancer Support Community, and National Cancer Institute, and the NCCN among many other organizations. Help and information, of course, is available through The Leukemia & Lymphoma Society, and we have an extensive array of both programs and services, including financial assistance through the copay, travel assistance, and medication access programs.

I've also included information here on identifying an information resource specialist, other programs, including our online chats, connection to the local chapter, the LLS community, which is an important social media platform, and our peer-to-peer program, the Patti Robinson Kaufmann First Connection Program. And we have a special program that provides 1:1 nutrition consultations through PearlPoint.



Slide 93 – In Summary

So that's a lot of information in a short period of time. And in summary, I always like to say that since much of our work comes down to communication, I borrowed this quote from Ellen Stovall. "With communication comes understanding and clarity, with understanding fear diminishes. In the absence of fear, hope emerges. And in the presence of hope, anything is possible."

Slide 94 – Thank you

Thank you so much.

Appendix 1

Table 2. Chronic Myeloid Leukemia (CML) Treatment Responses

Type of Response		Features	Test Used to Measure Response
Hematologic	Complete hematologic response (CHR)	• Blood counts completely return to normal • No blasts in the peripheral blood • No signs or symptoms of disease—spleen returns to normal size	Complete blood count (CBC) with differential
Cytogenetic	Complete cytogenetic response (CCyR)	No Philadelphia (Ph) chromosomes detected	Bone marrow cytogenetics or FISH
	Partial cytogenetic response (PCyR)	1% to 35% of cells have Ph chromosome	
	Major cytogenetic response (MCyR)	0% to 35% of cells have the Ph chromosome	
	Minor cytogenetic response	More than 35% of cells have the Ph chromosome	
Molecular	Complete molecular response (CMR)	No *BCR-ABL* gene detectable	Quantitative PCR (qPCR) using International Scale (IS)
	Major molecular response (MMR)	At least a 3-log reduction* in *BCR-ABL* levels or *BCR-ABL* 0.1%	

*A 3-log reduction is a 1/1,000 or 1,000-fold reduction of the level of cells with the *BCR-ABL* gene at the start of treatment.

Source: *The NCCN Clinical Practice Guidelines in Oncology™ for Chronic Myelogenous Leukemia, 2016.*

Table 2.This table describes the range of responses to CML treatment

Appendix 2

The International Scale (IS). This is a standardized scale for measuring qPCR test results. qPCR is a test that measures the number of cells that have the BCR-ABL gene. It is used to determine how well treatment is working. The International Scale defines the standard baseline as BCR-ABL 100 percent. This means that 100 out of 100 cells have the BCR-ABL gene. A log reduction indicates the BCR-ABL level has decreased by a certain amount from the standard baseline.

- 1-log reduction indicates that the BCR-ABL levels have decreased to 10 times below the standardized baseline. This means that 10 percent of cells (10 out of every 100 cells) have the BCR-ABL gene. This is also written as "BCR-ABL 10 percent." This reduction is equivalent to an early molecular response.
- 2-log reduction means that BCR-ABL levels have decreased to 100 times below the standardized baseline. This means that 1 percent of cells (1 out of every 100 cells) have the BCR-ABL gene. This is also written as "BCR-ABL 1 percent."
- 3-log reduction indicates that the BCR-ABL levels have decreased to 1,000 times below the standardized baseline. This means that 0.1 percent of cells (1 out of every 1,000 cells) have the BCR-ABL gene. This is written as "BCR-ABL 0.1%." It is also known as a "major molecular response" (MMR).
- 4.5-log reduction is referred to as a "complete molecular response" (CMR) or a "deep molecular response." Doctors may refer to this as "MR4.5." A 4.5-log reduction indicates that 0.0032% of cells (1 out of every 32,000 cells) have the BCR-ABL gene. Achieving a deep molecular response is a sign of disease remission. Patients who achieve and then sustain a deep molecular response for a significant period of time may be considered candidates for discontinuing drug therapy in a clinical trial.

qPCR tests may not be standardized from laboratory to laboratory. Different laboratories may establish their own standardized baselines. Consequently, the same sample may get slightly different results at different labs. Because of this, it is best to have samples sent to the same laboratory each time in order to receive consistent results. This will help patients and members of their healthcare team monitor patients' responses to treatment more effectively.
qPCR testing is recommended every 3 months for 2 years as long as the patient's CML is responding to treatment. After 2 years, the test should be done every 3 to 6 months.