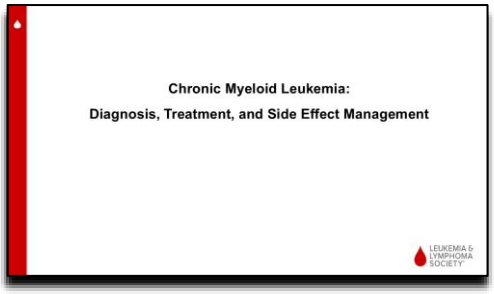
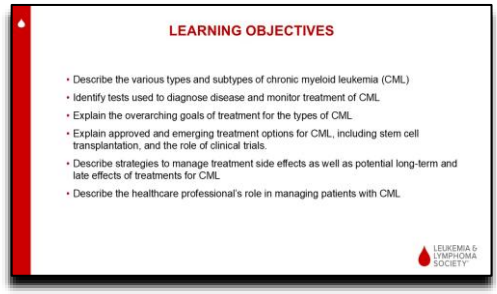


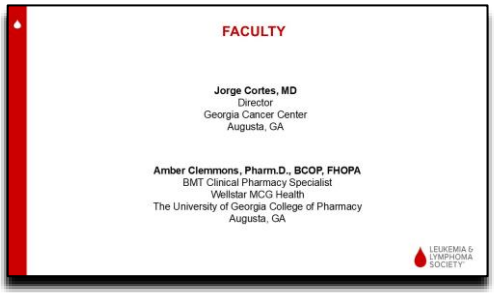
Slide 1: Chronic Myeloid Leukemia: Diagnosis, Treatment & Side Effects Management

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 & Side Effects Management.



Slide 2: Learning Objectives

The learning objectives are listed on this slide.



Slide 3: Faculty

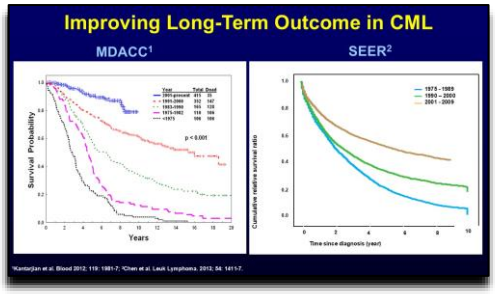
We're fortunate to have as our presenters Dr. Jorge Cortes, a leading expert in CML, and his colleague, Dr. Amber Clemmons, a Clinical Pharmacy Specialist. Dr. Cortes is Director, Georgia Cancer Center, in Augusta, Georgia.

Dr. Clemmons is Hematology/BMT Clinical Pharmacy specialist at Wellstar MCG Health, The University of Georgia College of Pharmacy, in Augusta, Georgia. We appreciate their dedication and their commitment to caring for patients living with blood cancers. Dr. Cortes and Dr. Clemmons, I am now privileged to turn the program over to you.

Slide 4: Disclosure Slide

Jorge Cortes, MD: Hello, my name is Jorge Cortes, and it's my pleasure to be here with you today to talk about where we are in chronic myeloid leukemia in 2024 since there's been a lot of new developments.

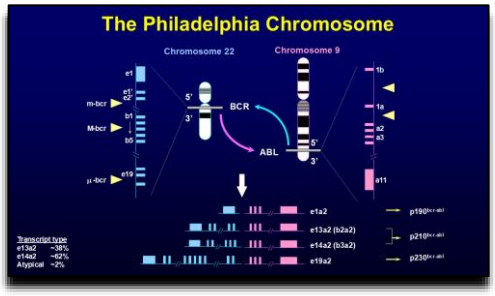
First, I wanted to present you with my disclosures.



Slide 5: Improving Long-Term Outcome in CML

And one important thing is to recognize that we have made a lot of progress in CML. This probability of survival has improved significantly from the 1970s when the Philadelphia chromosome was first discovered until now. But it is also clear that progress has not reached everybody. If you look at this slide at the improvement in survival in a selected institution where there's a lot of clinical trials, when there is a dedicated team and patients mostly get into medications, and monitoring through trials, the improvement is great.

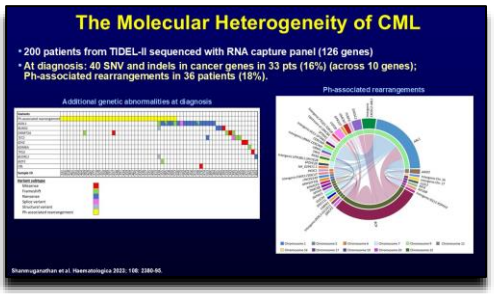
When you look at a more general population like the epidemiologic data from SEER on the right side, you see that there has been improvement, but it's not quite to the same extent that we see in these dedicated centers. So, that makes us first acknowledge that there is a lot of work that we need to do so that that benefit reaches everybody to the same extent.



Slide 6: The Philadelphia Chromosome

And you all know that what characterizes the chronic myeloid leukemia is the presence of the Philadelphia chromosome which is this balance switch in the genetic material between chromosomes 9 and 22 and that give rise to these fusion gene, half of a gene from chromosome 9 and half of a gene from chromosome 22. So that brings that fusion gene that we call BCR-ABL. So, when we are doing the test like the PCR, that's what we're looking at, this specific gene.

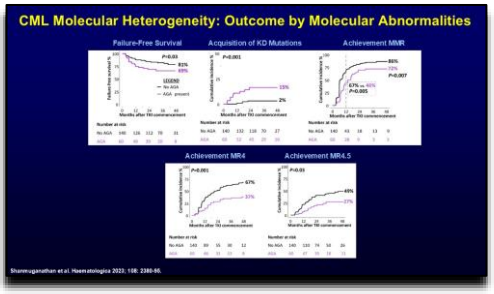
We also can look at the chromosome through the FISH and the chromosome analysis, but the main driver of this fusion gene, just an abnormal gene that's not present in normal cells or in individuals that don't have chronic myeloid leukemia. That is what represents the disease.



Slide 7: The Molecular Heterogeneity of CML

One important recent development is that we recognize that in addition to the Philadelphia chromosome, to this fusion gene, many patients at the time of diagnosis may have additional abnormalities in other genes that are frequently associated with other cancers. In about 15% of patients, we see these kind of abnormalities or what we call mutations in genes such as ASXL1 and TET1 and others. TET2 and others. But also rearrangements or changes in the chromosomes 9 or 22 but with other

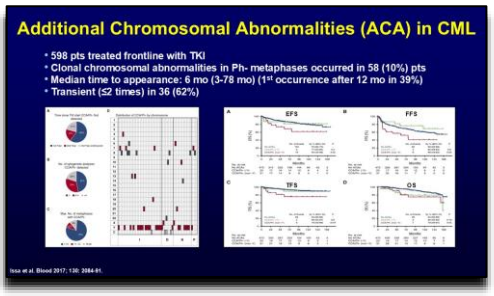
chromosomes, not among themselves. And there's another about 15% to 20% of patients that have these type of rearrangements.



Slide 8: CML Molecular Heterogeneity: Outcome by Molecular Abnormalities

What we've learned is that those patients that have these type of abnormalities have, number one, a lower probability of having a very good response to therapy. Doesn't mean it cannot happen. It's just a lower probability, but also a higher probability of progressing to a more advanced stage of their disease and accelerated phase, particularly a blast phase.

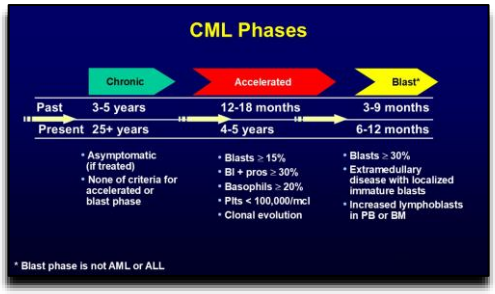
So this is important to know. Now, this is not the kind of test that we do on every patient at the time of diagnosis but on patients who are not responding well to treatment and we cannot explain the reason. Sometimes it's valuable to do this testing to see if that may be the reason why they're not having the response that we expect.



Slide 9: Additional Chromosomal Abnormalities (ACA) in CML

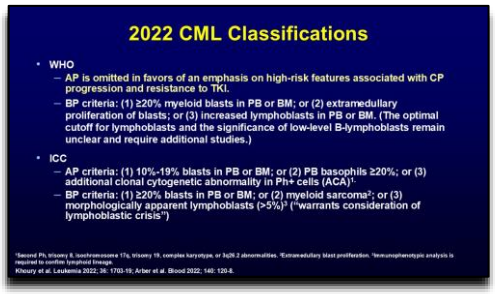
We also know that some patients have additional chromosomal abnormalities, meaning not only chromosomes 9 and 22 are involved, but other chromosomes, an extra chromosome 8, an abnormality in chromosome 17, or an extra set of chromosome, Philadelphia chromosome.

Sometimes this happens at the diagnosis. Sometimes it happens during treatment. One is as a manifestation of a failure of their treatment, but sometimes it also happens in the cells that now do not longer have the Philadelphia chromosome, in cells that we would expect to be normal but now have additional chromosomal changes. And these changes represent a lower probability of good survival in the long term. Also very important, and that is why sometimes we still emphasize doing bone marrow aspirations to look at the chromosomes and other characteristics of the bone marrow that you can only get through that particular testing as uncomfortable as it may be.



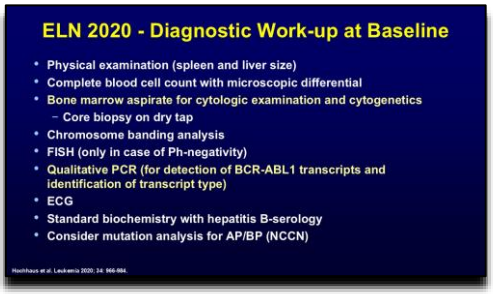
Slide 10: CML Phases

The chronic myeloid leukemia goes in through three different stages. Most patients nowadays are diagnosed in the chronic phase, which is very typically asymptomatic in many patients. They just find that their white cell count's elevated when they're getting a test for other reasons. And if you leave their disease untreated, essentially everybody's going to go to the blast phase. There is an intermediate stage that we have historically called the accelerated phase that signals that the chronic phase is starting to become more aggressive, but it's not quite at the stage of blast phase.



Slide 11: 2022 CML Classifications

There has been a little bit of controversy because we have two classifications now for chronic myeloid leukemia staging, one from the World Health Organization, or the WHO, and the other one is the ICC, or the International Consensus Classification. The WHO now states that there is no accelerated phase. They instead emphasize high-risk features associated with the chronic phase when it's progressing, when it's not responding to therapy, whereas the ICC still recognizes the accelerated phase. In my view, this is more semantics. The WHO says, "Well, it doesn't have to have the features that we historically called the accelerated phase. There are some patients still in chronic phase by those features, but they are moved forward, for example, because they're not responding to therapy; and that'll really represent a stage beyond the classic stable chronic phase."

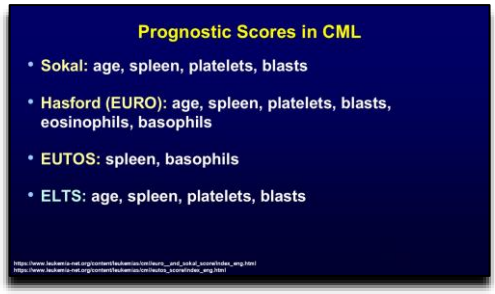


Slide 12: ELN 2020 - Diagnostic Work-up at Baseline

We, I mentioned earlier that I still think that the bone marrow aspiration is needed on every patient. That's the only way that you can do a full analysis of all the characteristics of the disease. I can diagnose the disease without a bone marrow, but I cannot learn all the characteristics of their disease if I don't do a bone marrow aspiration and a biopsy. So, I still like to do a bone marrow aspiration on all my patients.

Also important to remember that the PCR is a valuable test. At diagnosis, the value doesn't tell us anything, but it is important because there are some patients that have unusual rearrangements between the BCR and the ABL that are not picked up by the PCR that we do in the clinic. So, doing it at the time of diagnosis will tell me if I am going to be

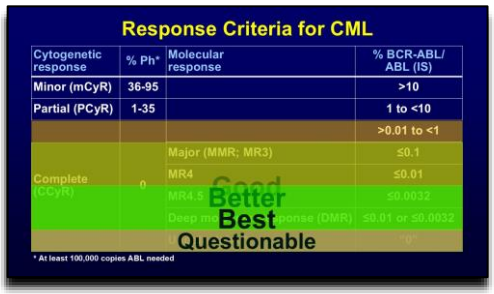
able to monitor that patient through a PCR, which is a large majority of patients, the overwhelming majority of patients or not. In which case, I have to rely on the cytogenetics and the FISH.



Slide 13: Prognostic Scores in CML

We also do some prognostic scores that are based essentially on age, spleen, platelets, blasts. There are different classifications that we use: the Sokal, the Hasford, the EUTOS. More and more we're transitioning to one that's called the ELTS. They're all very similar, and they require some formulas that you can find on websites. But it is useful just to see what are the probabilities of responding and progressing and so on?

Most patients in the US and in the Western countries are in the low or intermediate classification. Very few are in the high risk, although in Latin America and Africa and Asia, we do see more patients that are diagnosed in the more advanced stages, in the high-risk stages.

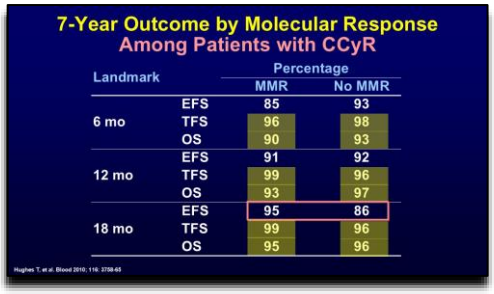


Slide 14: Response Criteria for CML

Very important is to know the response criteria for CML. We measure that historically by the chromosome analysis or by FISH. More and more we rely on the PCR. But there is some equivalence between these classifications. Historically, we've looked at a partial cytogenetic response, which is very similar to having a PCR of less than 10%, and then a complete cytogenetic response, which is when you get to 1% or less. And then from there, deeper responses, major molecular response, 0.1; MR4, 0.01; and MR4.5, 0.0032.

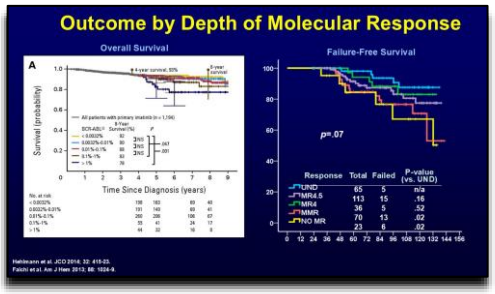
Very important to recognize that already a complete cytogenetic response of less than 1 is a good response. That correlates within essentially a normal life expectancy. Now, of course, the major molecular response is better. Yeah, it decreases it's probability of progression; and even more, the deeper molecular responses, particularly MR4.5 are the best because those are the ones where we can start talking about treatment interruption. Treatment-free remission.

Undetectable is very tricky because it depends on the quality of each sample; and it may be that it is undetectable because there was not enough DNA in the sample. So, you have to be very cautious about using undetectable unless you know exactly what is the power of that particular test on that particular date.



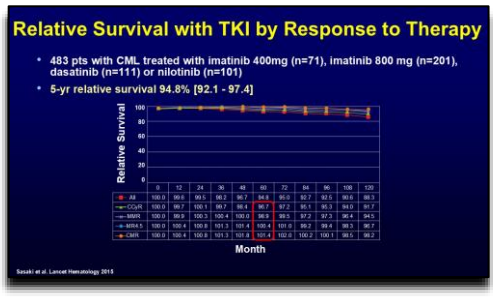
Slide 15: 7-Year Outcome by Molecular Response Among Patients with CCyR

Now, I mentioned that having a major molecular response is important because it correlates with having a lower probability of losing response eventually and progressing to accelerated or blast phase, what we call an event-free survival. That is within patients that already have a complete cytogenetic response. It doesn't correlate with survival or with transformation-free survival. Remember, I mentioned the overall survival really was you get to a complete cytogenetic response is what correlates with an improved survival.



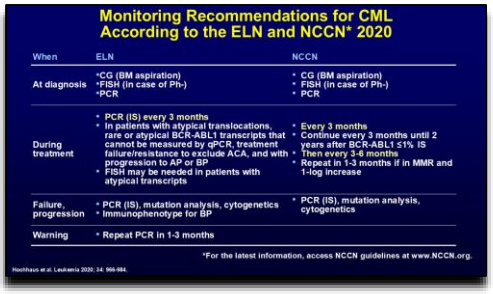
Slide 16: Outcome by Depth of Molecular Response

The deeper responses are also going to improve the survival. You see that the, the survival is very similar if you talk about patients in complete cytogenetic response. Survival is the same, even if you go to the MR4s and MR4.5s. The failure-free survival, meaning surviving without, eventually losing their response, it may be better if you have a deeper molecular response. But, of course, the main benefit of the deeper molecular responses is the probability of considering treatment-free remission.



Slide 17: Relative Survival with TKI by Response to Therapy

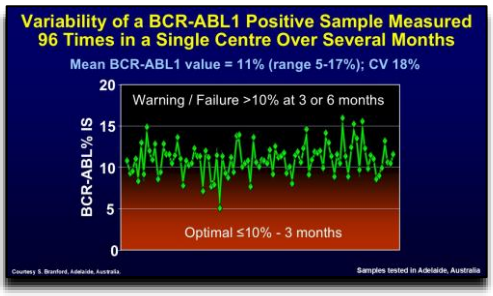
In any case, as I mentioned earlier, what we have now is that for patients who have access to treatment, to monitoring, who are managed well, the life expectancy today for a patient with CML is nearly the same as that of the general population, of somebody who's of the same age, the same sex, etc. So, that is important to remember. But it all depends on adequate management of the patient and good monitoring and all of the elements that constitute proper management of a patient with chronic myeloid leukemia.



Slide 18: Monitoring Recommendations for CML According to the ELN and NCCN 2020

Well, as I was mentioning, it is important to remember how do we monitor a patient? I mentioned that at diagnosis, I want to do a bone marrow. I want to do cytogenetics, FISH and PCR. And, all the guidelines I'm showing you here is some of the most commonly used – ELN and NCCN – recommend that.

During treatment, a PCR is recommended every three to six months. It is not recommended to do more frequent than that; and I'll tell you more on the next slide about that. So every three to six months is sufficient. I usually do it every three months, and once the patient has a stable, good response, every six months tends to be more than enough.



Slide 19: Variability of a BCR-ABL1 Positive Sample Measured 96 Times in a Single Centre Over Several Months

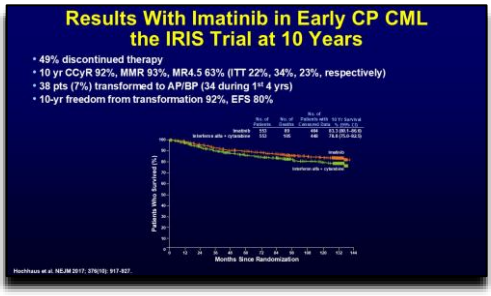
And I mentioned that doing the test more frequent is not very useful. It can be actually confusing. This slide represents an experiment that was done with one sample, obtained from one patient on a given day. And then with that one tube, was separated into 96 small samples from the same patient, the same day, the same drug, the same draw, the same lab.

And then they were measured at different times, and you can see the big variability that you can observe in the results. So, when you're doing tests very frequently, you can see this variability that can be confusing and doesn't lead to any benefit; or it could actually cause confusion and create the need to change therapies when there's not a good indication to do that. So, again, I almost never do the PCR more frequent than every three to six months.

Slide 20: ELN 2020 Treatment Recommendations

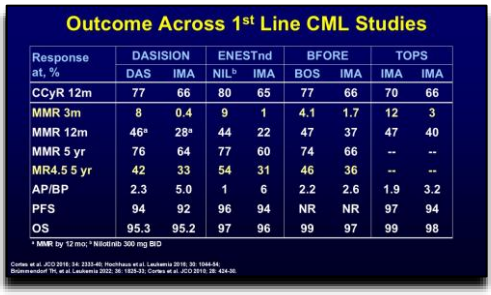
The treatment recommendations have evolved, but we all know that today as initial therapy, there are four drugs that are approved for initial therapy for tyrosine kinase inhibitors. Imatinib (Gleevec®), what we call the first-generation TKI and then dasatinib (Sprycel®), nilotinib (Tasigna®), and bosutinib (Bosulif®), which we call the second-generation TKIs. Of course, we do have generic imatinib (Gleevec®), which is also recommended. This is the generic that we have available in the US. And then for subsequent lines of therapy, we

have two additional drugs, two additional TKIs, ponatinib (Iclusig®) and asciminib (Scemblix®), both of them indicated for patients who have received two prior TKIs or who have the mutation T315I.



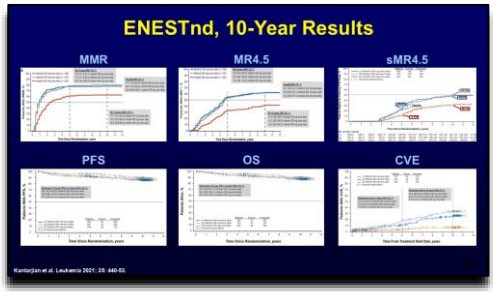
Slide 21: Results With Imatinib (Gleevec®) in Early CP CML The IRIS Trial at 10 Years

Imatinib (Gleevec®) was the first one that was developed; and it was the first one that came to be used as initial therapy for CML. And we already learned that it was incredibly superior than interferon (Intron® A) which was the standard of care at the time. But also, it improved the survival probability of the patients. Even when eventually everybody received imatinib (Gleevec®), just the fact that those patients were started with imatinib (Gleevec®) from the beginning, they had a better probability of survival.



Slide 22: Outcome Across 1st line CML studies

Then came the second-generation tyrosine kinase inhibitors, dasatinib (Sprycel®), nilotinib (Tasigna®), and bosutinib (Bosulif®). In the three studies that you see here, DASISION, ENESTnd, and BEFORE, and what these studies showed us is that with the second-generation TKIs, you get a higher probability of responses. You get more early responses, particularly at three months. You get deeper molecular responses, more MR4s and MR4.5s. You get fewer patients that go into accelerated or blast phase. What you don't see is an improvement in progression-free survival or in overall survival because without imatinib (Gleevec®), again, you already get pretty close to a normal life expectancy.



Slide 23: ENESTnd, 10-Year Results

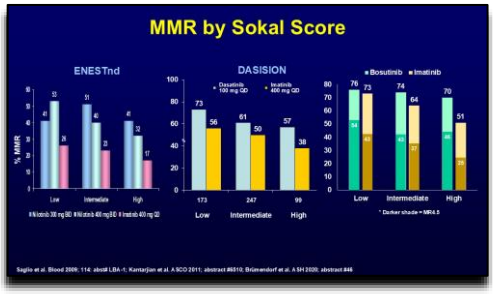
I'm going to show you the results of one of these studies, the one from nilotinib (Tasigna®) compared to imatinib (Gleevec®); and the reason I'm showing this is because this is the one where we have the longest follow-up. We have ten years of follow-up data, and it helps us to illustrate a few things that are very important.

Number one is that you can see that the major molecular response is achieved in a significant number of patients, but not in everybody. Only about 80% of patients will ever get to a major molecular response. And you see that by five years you already reached a

plateau. Now, if you use imatinib (Gleevec®), that percentage is lower. It's, closer to a 60% probability.

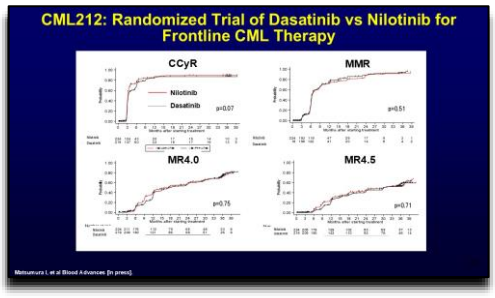
And the deeper molecular responses happen even less frequent. You see by ten years, it's about 60% of patients with nilotinib (Tasigna®). Only about 40% with imatinib (Gleevec®). And it's also reached a plateau. After seven, eight years, you don't see much more of an increase in the probability.

But even more important, for treatment-free remission, what we need is these responses to be sustained for at least two years. And you can see that only about half of the patients will ever get to that level, and that's with nilotinib (Tasigna®). With imatinib (Gleevec®), again, it's lower. Now, you can see at the bottom progression-free survival, PFS very similar between the three, between nilotinib (Tasigna®) or imatinib (Gleevec®). Overall survival, very similar. But also, arterial occlusive events, much more common with nilotinib (Tasigna®) than with imatinib (Gleevec®). And I'll talk more about this in a minute.



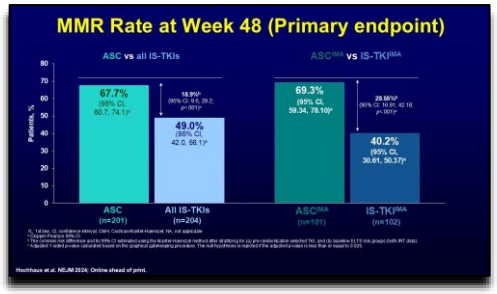
Slide 24: MMR by Sokal Score

It's also said that the choice of imatinib (Gleevec®) versus second-generation TKI could be driven by the Sokal Score where the patients with the highest Sokal Score are the ones where you would choose a second-generation TKI. However, when you look at the data from all these studies, it is very clear that although certainly the patients with high risk benefit, and there's probably the biggest need for that improvement, there is a benefit even for patients that have low or intermediate risk Sokal classification risk. So, I think that every patient is a good candidate for a second-generation TKI; and they will get the benefit that I described earlier.



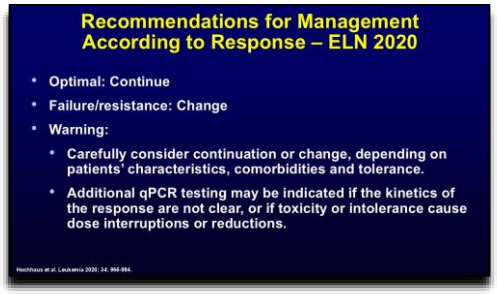
Slide 25: CML212: Randomized Trial of Dasatinib (Sprycel®) vs Nilotinib (Tasigna®) for Frontline CML Therapy

The second-generation TKIs had not been compared head-to-head until very recently, but in this study that was done in Japan, patients with new diagnosis of CML were at random assigned to receive either nilotinib (Tasigna®) or dasatinib (Sprycel®). And as you can see, they gave essentially the same results, the same probability of response, whether it's complete cytogenetic response, major molecular response, MR4, MR4.5. So, really from the point of view of efficacy, these are all very similar drugs. Their safety profile varies and other characteristics that can help us define which drug may be better for a given patient.



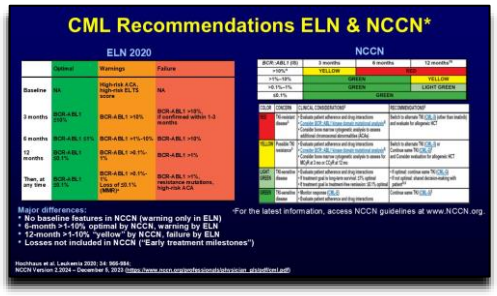
Slide 26: MMR Rate at Week 48 (Primary endpoint)

Very recently, there was a study that was just announced where asciminib (Scemblix®) was compared to all the tyrosine kinase inhibitors that are approved for initial therapy. And it showed that you can get a much higher rate of major molecular response at one year with asciminib (Scemblix®) than with all the TKIs and certainly than with imatinib (Gleevec®). Now asciminib (Scemblix®) today is not approved for initial therapy. This data is being evaluated by the FDA. They will decide if this gets the approval or not, but these results are certainly very interesting.



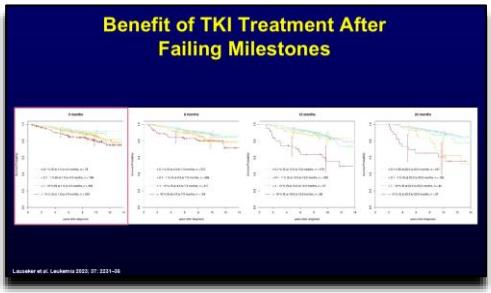
Slide 27: Recommendations for Management According to Response – ELN 2020

The patients that have treatment, we monitor them with a frequency that I mentioned earlier. And they can have what we call an optimal response, a failure or a resistance, or a warning. When they have optimal response, you continue the same treatment. When there's failure, you change. When there's a warning, it's an intermediate category; and usually we continue to monitor, just more frequently, more closely. Although in some instances, a change could be indicated.



Slide 28: CML Recommendations ELN & NCCN

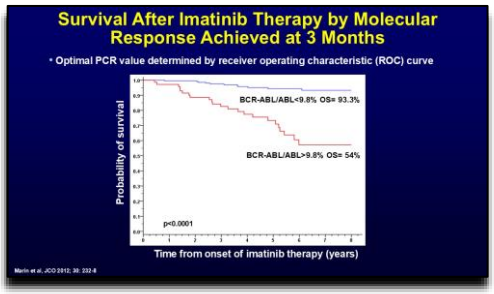
This is shown here what constitutes these optimal warning or failure. It depends on the response that the patient is having at the three, at the six, at 12 months and then later on. They're very similar between the different recommendations. Here you see the ELN and NCCN. Very mild variations, but essentially they tell us the same.



Slide 29: Benefit of TKI Treatment After Failing Milestones

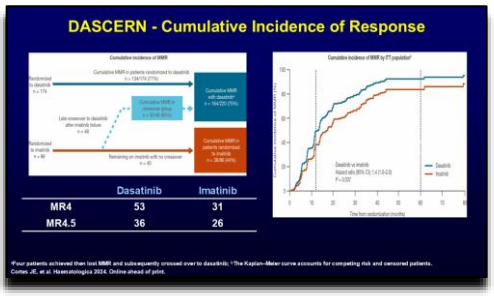
One important thing, however, to consider is that in the early timepoints, even patients who are not meeting the desired endpoints, they still have a very good probability of survival. So, that is why in the first three to six months we are less anxious to change therapy, even in these patients that are moving a little slower because they still can catch up and do very well and have the same probability of survival. By 12, 24 months, the need for change

becomes more clear because the probability of survival goes down significantly. So, I'm just highlighting here that three-month data that I was telling you about.



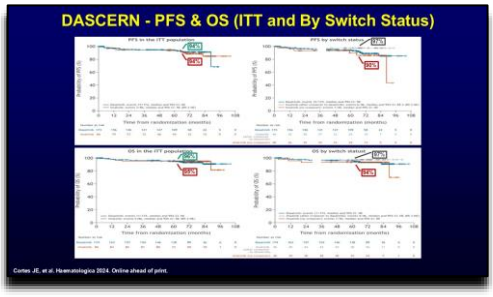
Slide 30: Survival After Imatinib (Gleevec®) Therapy by Molecular Response Achieved at Three Months

Now, many years ago, we established that those patients that at three months had more than 10% transcripts had a lower probability of survival. Now here it shows a big difference because this predates the wide availability of second-generation TKIs. But it is clear that they have a worse prognosis. The question is, what do you do if you have a patient that has more than 10% at three months? So, the initial idea was, well, you need to change.



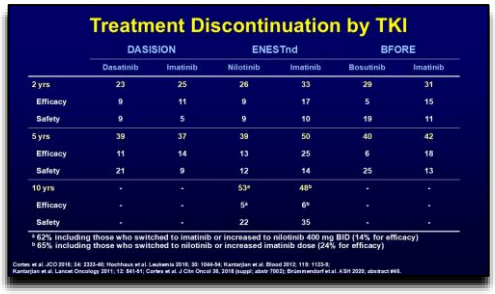
Slide 31: DASCERN - Cumulative incidence of Response

But we did a study that included patients that were receiving imatinib (Gleevec®) and had more than 10%, and they were randomized to receive either dasatinib (Sprycel®) or imatinib (Gleevec®). And you can see here that although the probability of getting a major molecular response was better for the patients who switched to dasatinib (Sprycel®), the benefit is relatively small. You know, it is a gap there; but it is relatively small.



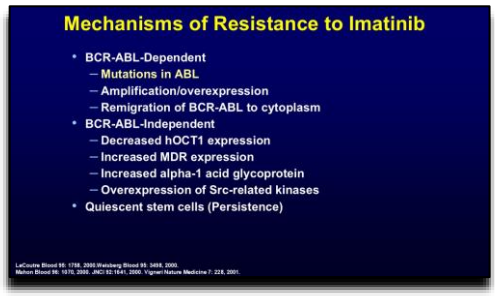
Slide 32: DASCERN - PFS & OS (ITT and By Switch Status)

But more important, there was no difference in progression-free survival and no difference in overall survival. So really today, we don't recommend to change at three months because we don't see that there is a real change; and you may just be exposing patients to side effects that they may not have been experiencing with their, with imatinib (Gleevec®).



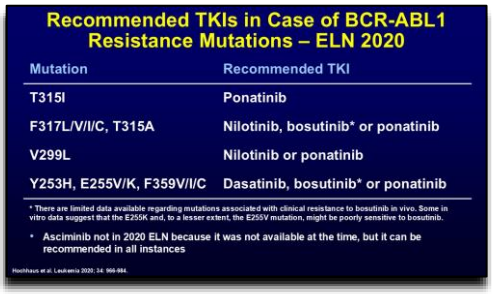
Slide 33: Treatment Discontinuation by TKI

Ultimately, however, we do know that many patients will need to change therapy. Going back to those studies that compared the second-generation TKIs to imatinib (Gleevec®), you see that at five years essentially 40% of patients have changed therapy, either because of efficacy or because of safety. But there has been a high need for change in therapy because of, the treatment didn't do what we expected it to do.



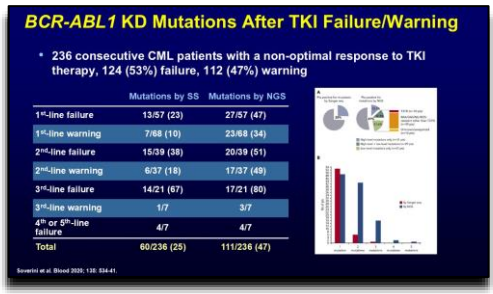
Slide 34: Mechanisms of Resistance to Imatinib (Gleevec®)

The most common reason why patients don't have the response that we expect is because of mutations. Mutations in what we call the ADL kinase domain in the site where these drugs bind. There are other mechanisms of resistance, but these are more of our research elements that we don't really measure in the clinic. There's no good way to measure them in the clinic. So, for many patients, we don't know what the mechanism of resistance is.



Slide 35: Recommended TKIs in Case of BCR-ABL1 Resistance Mutations – ELN 2020

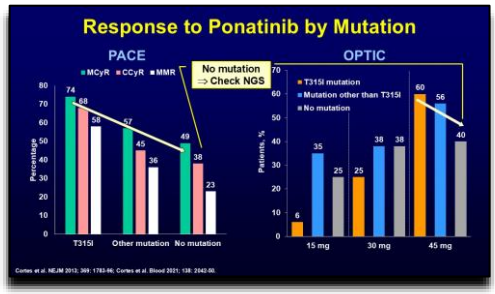
But when they have a mutation, that can guide us to select what may be the drug that may be better suited for individual patient. Now, keep in mind that only a few of the mutations really guide us in that regard. For most of the mutations, there's no good difference between one drug and the other they still don't become informative as to what drug you need to use. We use other parameters, including the, the safety profile of the drug, the experience in that scenario, etc. to select the drug.



Slide 36: BCR-ABL1 KD mutations After TKI Failure/Warning

It is also very important to remember that when a patient develops resistance to a tyrosine kinase inhibitors and we check for mutations, we will only find mutations in about 25% of patients. That is by using the test that we use more frequently in the clinic. If you use a more powerful test that is not the one that we always use, not even half of the patients

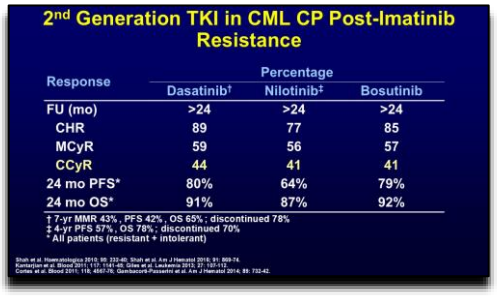
are going to have a mutation detectable, even though the test is more powerful. So, keep in mind that when there is resistance, there is not always a mutation that we can identify.



Slide 37: Response to Ponatinib (Iclusig®) by Mutation

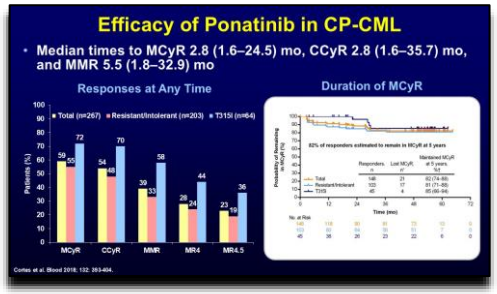
And this is very important because although we sometimes are scared of having a mutation, when you look at the results, for example, in this study of ponatinib (Iclusig®), a very good drug that works well in patients that have received two or more tyrosine kinase inhibitors, you can see that the patients that have the lowest probability of response are the patients that have no mutations. So, really what matters is not so much that you have a mutation or not. It is whether you had resistance. And if you don't have a mutation, we still have a question of what caused the resistance and what do we do? What's the best approach for these patients?

This is one of those scenarios where I would do one of these tests that I mentioned at the beginning where you can find mutations in other genes that are associated with, with cancer. And many times you will find those kind of mutations.



Slide 38: 2nd Generation TKI in CML CP Post-Imatinib (Gleevec®) Resistance

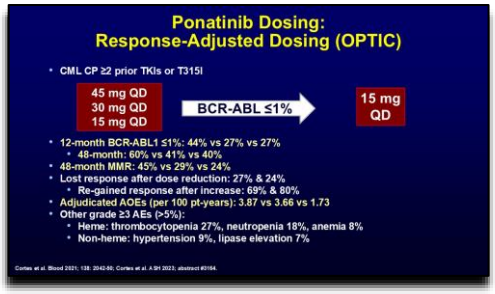
Once you identify that a patient has had resistance, you can use another TKI. Now, we have a lot of good options, and they work well. But you can see here that patients that are taking a second-generation TKI, after only imatinib (Gleevec®), you get a response in about 40% of the patients. And that's a complete cytogenetic response only. So, it is very important to do very good treatment, very good management of the patient, optimal doses to maximize the probability of having a good response to therapy.



Slide 39: Efficacy of Ponatinib (Iclusig®) in CP-CML

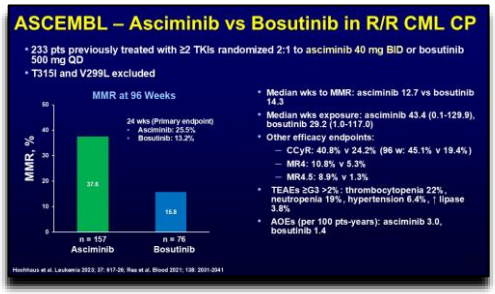
Now we have now third-generation drugs like ponatinib (Iclusig®). In this study, the patients that had received two or more, but actually the majority, three or more tyrosine kinase inhibitors, we saw a very good probability of response with major cytogenetic responses of almost 60%. And even some deeper responses, and these were very durable. However, we learned very soon

that with ponatinib (Iclusig®) you could see what we call arterial occlusive events. These are events such as heart attacks or angina, strokes, or transient ischemic attacks in the brain, or an occlusion of the arteries in the extremities, which can cause gangrene and other things.



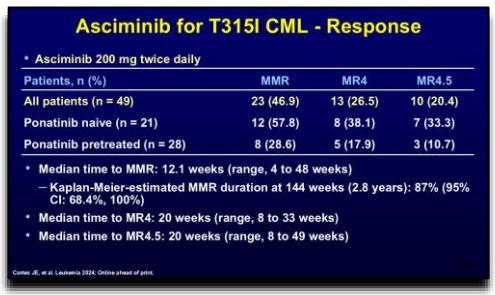
Slide 40: Ponatinib (Iclusig®) Dosing: Response-Adjusted Dosing (OPTIC)

So, in trying to minimize that risk, there was a study that looked at the different ways of using ponatinib (Iclusig®). First, it looked at whether using lower doses as a starting dose would reduce the risk. But also, that when you achieve the response, you would lower the dose anyway, even if you were taking the standard dose of 45 milligrams daily. So what did we learn from this study is that 45 milligrams, which is the standard dose, is still the most effective. But by lowering the dose once you achieve a response, you decrease significantly the risk of these arterial occlusive events, the heart attacks and strokes and these things significantly. So, that is the way that we manage ponatinib (Iclusig®) nowadays.



Slide 41: ASCEMBL – Asciminib (Scemblix®) vs Bosutinib (Bosulif®) in R/R CML CP

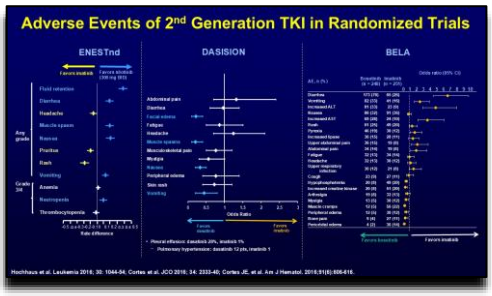
There's a newer drug that's also kind of a third- or a fourth-generation TKI called asciminib (Scemblix®), and this was used in a group of patients also that had received more than 2 TKIs; and they were compared directly, to bosutinib (Bosulif®). So, some patients took bosutinib (Bosulif®), some patients took asciminib (Scemblix®); and it showed that clearly asciminib (Scemblix®) was superior than bosutinib (Bosulif®) in this context. It had a little bit more of arterial occlusive events than bosutinib (Bosulif®) which has historically very few. But it was not a very high rate. It was just a little bit higher than bosutinib (Bosulif®).



Slide 42: Asciminib (Scemblix®) for T315I CML – Response

Now in this study, patients with a T315I mutation were not included, but there was a separate study that looked at those patients treated with asciminib (Scemblix®); and we saw that there were very good responses. Almost half of the patients got a major molecular response. It's a little bit lower if the patient had already received ponatinib (Iclusig®), but it's still a very good, almost 30% response.

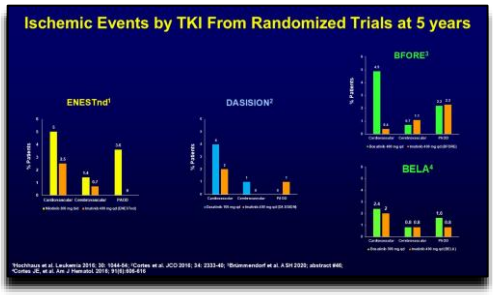
What's very important is that for patients that have these mutations, the T315I, the dose of asciminib (Scemblix®) is five times higher than if they don't have the mutation T315I. So the dose here is 200 milligrams twice daily. For every other patient, it's 40 milligrams twice daily or 80 milligrams once daily.



Slide 43: Adverse Events of 2nd Generation TKI in Randomized Trials

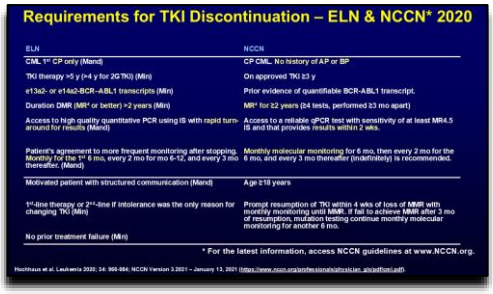
You all know that the different drugs have different side effects. Some of them are common. They can all drop the counts they need, the platelet count, the neutrophils, etc. Some of them are more unique, but it's always good to know and to understand these potential side effects so that you can tailor the drug to what may be more manageable for our given patient based on their characteristics and medical history and so on. And also explain and manage it with the patient so that they are prepared to see what are the kinds of things that they could see.

So, we see that, for example, with nilotinib (Tasigna®). We see rashes and headaches and elevation of bilirubin. With, dasatinib (Sprycel®) we see pleural effusion. We see bloating. We see elevation of the blood pressure of the pulmonary arteries. With bosutinib (Bosulif®) we see transient diarrhea, liver test abnormalities, some rashes, and so on. You will hear a little bit more about this, how we manage these side effects.



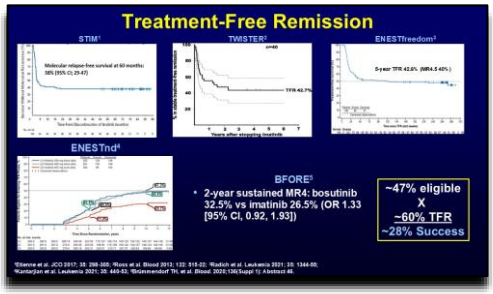
Slide 44: Ischemic Events by TKI From Randomized Trials at Five Years

One of the side effects that is more important, that I talked about earlier, is the arterial occlusive events. We know that nilotinib (Tasigna®) and dasatinib (Sprycel®) have twice the risk than imatinib (Gleevec®). So, very important to recognize that patients that have comorbidities, if you're going to be using these drugs, you need to manage the comorbidities. That means manage the blood pressure, manage the diabetes, manage the cholesterol. Stop smoking. A balanced diet. Good exercise. You know, all these things that decrease the risk of arterial occlusive events so that you can minimize the risk. Bosutinib (Bosulif®) has a little bit higher risk, than imatinib (Gleevec®), but not as low as imatinib (Gleevec®) and not as high as nilotinib (Tasigna®) or dasatinib (Sprycel®).



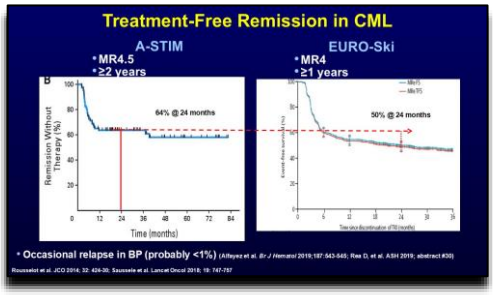
Slide 45: Requirements for TKI Discontinuation – ELN & NCCN 2020

Now coming to the last few things, one important thing to remember, I mentioned earlier, is the possibility of treatment discontinuation. To do this, today we recommended only for patients who are in chronic phase; never been in accelerated phase or blast phase; who have the typical transcripts, which is the majority of patients, but those are the ones that you can measure by PCR; that have had a deep molecular response for at least two years in a row; and where you can monitor very frequently once we stop the treatment.



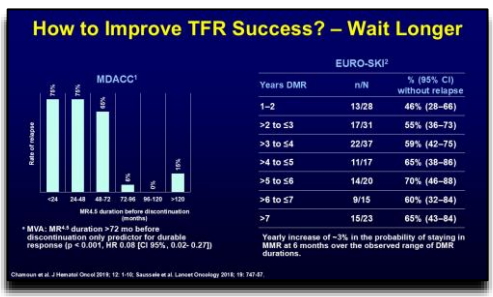
Slide 46: Treatment-Free Remission

When you do that, we know that about 50% of patients will be able to remain free of treatment. The other 50%, they will have to resume therapy. Usually they respond well, but they will need to continue on treatment. But keep in mind that I mentioned early, only about 50% of patients meet the criteria that I just mentioned. Out of them, 50% will relapse, so that means that grossly about 25% to 30% of patients that are treated with TKIs today we can do successful treatment-free remission. Many other patients can have a normal life expectancy and live well, but they will need to continue with the treatment.



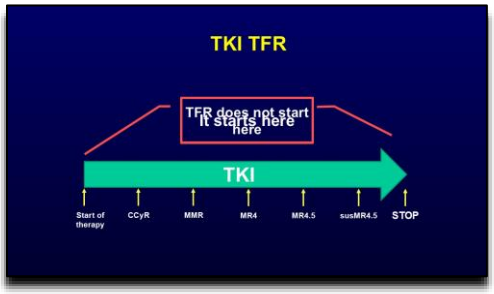
Slide 47: Treatment-Free Remission in CML

Now to try to improve this, there have been different approaches. One of them is to relax the rules. Instead of doing with MR4.5 that has been sustained for two years, do it with MR4 sustained for only one year. But the problem is you don't get the same results. You get more patients to lose their response when you stop therapy, so that is not the solution. Yeah, you can stop it in more patients; but more patients relapse.



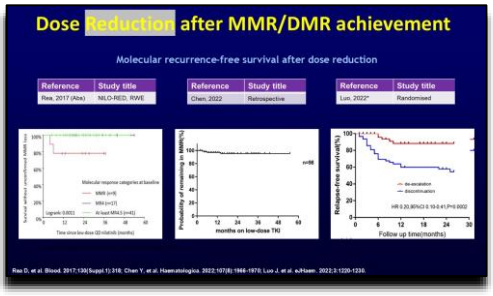
Slide 48: How to Improve TFR Success? – Wait Longer

The other approach is to wait longer. So, instead of only doing it after two years, if you wait for six years, the probability of losing their response goes down significantly. So, my recommendation usually is at least two years but ideally six years in a sustained MR4.5 makes it much more likely to be effective at treatment discontinuation.



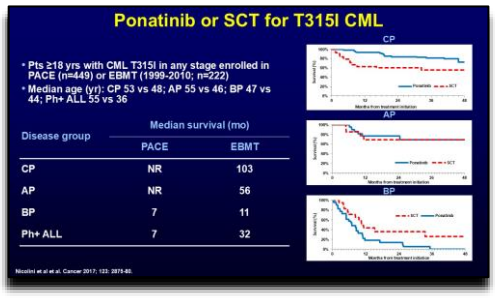
Slide 49: TKI TFR

The one thing that I wanted to remind to all my patients and my colleagues is when you see a patient with CML and you start the treatment and you start seeing all the evolution of therapy, you hopefully get to the deep molecular response, to the sustained deep molecular response where you can stop therapy. I remind everybody that the TFR does not start when you stop therapy. TFR starts on the very first day that you diagnose a patient because proper management, taking the medication, monitoring well, managing comorbidities, that is what makes a patient in the best position possible to eventually get to stop therapy. And still then, not everybody's going to get there; but I've given the patient the best chance of being there.



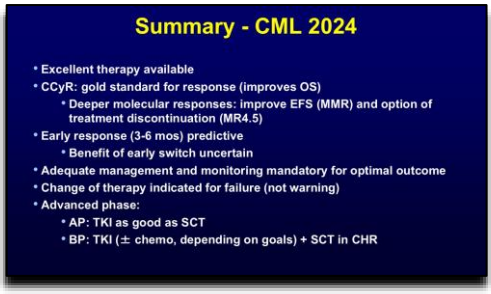
Slide 50: Dose Reduction after MMR/DMR Achievement

Now for the patients who cannot stop therapy, what we've learned is that you can lower the doses; and many patients are able to maintain a very good response but with much lower doses. And that's beneficial because you have fewer side effects; patients tend to tolerate that better. So, for the patients where I cannot stop therapy, at least I can offer them the possibility, to many of them, not everybody, but to many of them to lower the dose to the minimum effective dose that will maintain a good response with the fewer side effects.



Slide 51: Ponatinib (Iclusig®) or SCT for T315I CML

Finally, I wanted to remind you that stem cell transplantation is still a valid option, still an important option. We don't use it as initial therapy most instances. But for patients who have had many therapies before, it is a good option. Now, you have to always balance the risks, the benefits, the characteristics of the patient. In this study, for example, we looked at the patients that had the T315I mutation and see what the outcome could be if they receive ponatinib (Iclusig®) or if they received a transplant. In the chronic phase, they actually do better if they get ponatinib (Iclusig®). In the accelerated phase, the outcome is very similar. In the blast phase, you definitely need a transplant. Usually, you want to get some treatment to get the patient into a, back into chronic phase but always do a transplant.



Slide 52: Summary - CML 2024

So, to conclude, I will just remind you that we do have excellent therapy in 2024 for patients with CML. Most patients get what I consider the gold standard for a response, a complete cytogenetic response. And a majority of patients will get to the deeper responses. So, we always aim for the deep molecular responses but not getting there is not a failure. It's a goal, but it's not a failure. I call it a measure of success, not a measure of failure.

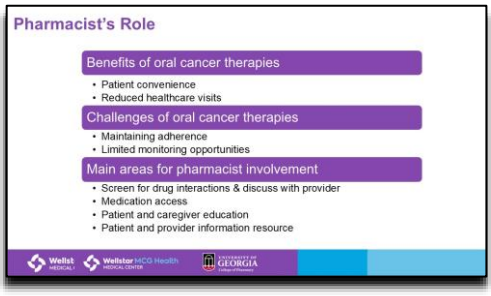
But very importantly, adequate management and monitoring gives the patient the best probability of getting to the deeper molecular responses; and managing the side effects, managing the comorbidities will minimize the risks for the patient in the long term.

Slide 53: Questions

So, with that, I conclude my part of the presentation; and I'm going to turn it over to Amber, who can tell us more about the prospective of a pharmacist on the management of these drugs. Thank you very much for your attention.

Slide 54: Pharmacist Role in Managing Patients with Chronic Myeloid Leukemia

Amber: Hello and thank you for participating in today's educational program. I'll be discussing the role of the pharmacist in the management of patients with chronic myeloid leukemia.



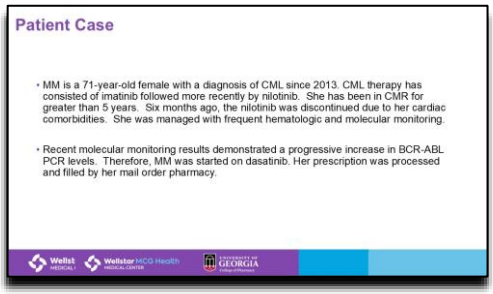
Slide 55: Pharmacist's Role

Oral therapies have a number of benefits. Patients enjoy the convenience of having an at-home therapy they can self-administer as compared to having to receive their care in a hospital or in a clinic setting. So, they do require fewer healthcare visits, such that their day-to-day life is less impacted. They can continue to attend work or school, for example.

However, despite these benefits, there are a number of challenges that exist with oral cancer therapies. It is much more difficult to assess and confirm adherence in these

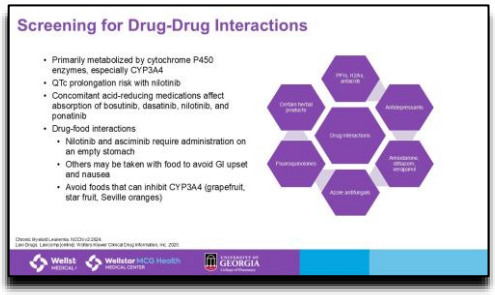
settings as compared to a clinic where a nurse is administering and documenting the administrations whereby that can be confirmed by a provider. Also, with the fewer healthcare visits, there are fewer opportunities to monitor these patients on these oral therapies. Given the benefits and limitations with these treatments, I'll be discussing the main areas where a pharmacist can be involved in the care of these patients.

First, we'll discuss screening for interactions, then assisting patients with accessing these high-cost products, as well as talk about how a pharmacist can educate and serve patients and providers alike as a drug information resource.



Slide 56: Patient Case

First, let's start with a brief patient case. We have MM, a 71-year-old female who has a long history of CML, since 2013. She initially was treated with imatinib (Gleevec®) therapy and then most recently with nilotinib (Tasigna®). But that was discontinued due to cardiac comorbidities as she had been in a CMR for more than five years. She was being followed with frequent hematologic and molecular monitoring. Unfortunately, recent results revealed a progressive increase in her BCR-ABL PCR transcripts and, therefore, she was provided a prescription for dasatinib (Sprycel®). It was sent to her mail order pharmacy as required by her insurance. Keep MM in mind because we're going to come back to her in a few moments.



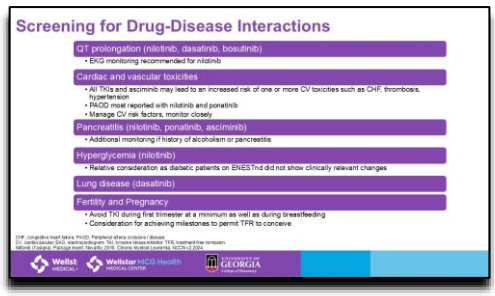
Slide 57: Screening for Drug-Drug Interactions

As with any drug therapy, screening for interactions is very important. For the TKIs, this is especially crucial as there are many drug interactions. Most patients with CML are older in age so they have or can develop new comorbidities over time that require various concomitant medications. All of the BCR-ABL TKIs and asciminib (Scemblix®) are metabolized through cytochrome P450 enzymes and, in particular, CYP3A4. As substrates of this enzyme, these agents are impacted by many common medications that are moderate to strong inhibitors or inducers of this enzyme. Beyond the CYP enzymes, each oral chemotherapy agent also has other interactions to consider. For example, agents that also increase QT prolongation risk could be a concern with agents such as nilotinib (Tasigna®). Beyond our drug-drug interactions, we also need to consider drug-food interactions and counsel our patient on this information.

Concomitant acid-reducing medications such as proton pump inhibitors and even oral, over-the-counter oral agents like calcium carbonate can decrease exposure to our TKIs such as bosutinib (Bosulif®), dasatinib (Sprycel®), nilotinib (Tasigna®), and ponatinib

(Iclusig®); and, therefore, patients need to be educated on this interaction and either to avoid or separate them out, depending on which of these drugs we're discussing.

Further, nilotinib (Tasigna®) and asciminib (Scemblix®) must be taken on an empty stomach to be effective while the other agents may be taken with food to reduce GI upset. And lastly, patients need to understand any drug-food interactions. There are some products that we can ingest that impact cytochrome P450 3A4. These include grapefruit, star fruit, and Seville oranges, which patients should be counseled to avoid consuming while on these medications.



Slide 58: Screening for Drug-Disease Interactions

In addition to reviewing a patient's medication list for interactions, the pharmacist also reviews the patient's comorbid conditions to see if there are any interactions or potential concerns. Here we see just a list of some of the examples. There could be other conditions or potential overlapping toxicities that may also require increased awareness or a management plan.

As previously mentioned, these TKIs, nilotinib (Tasigna®) in particular, have a risk for QT prolongation. So, if a patient had a history of long QT syndrome, this would be something the provider would need to consider when selecting an agent. As Dr. Cortes has mentioned previously, as we gain further experience with these agents, we are now having an increased understanding of long-term toxicities, such as those very important cardiovascular toxicities that are coming to light. All of these agents can be associated with a higher risk of one or more cardiovascular toxicities such as congestive heart failure, hypertension, or thrombotic events just to name a few.

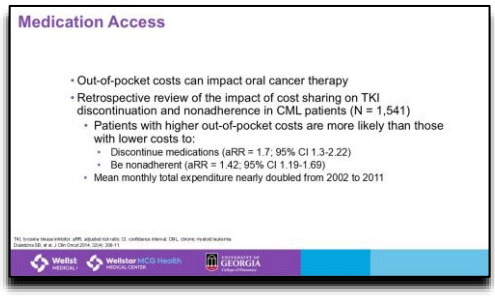
Specifically, nilotinib (Tasigna®) and ponatinib (Iclusig®) are associated with the increased risk of those peripheral arterial occlusive disease that have been recently mentioned in this presentation.

As patients may be on these agents for life, it is important that pharmacists and providers assist patients in managing those cardiovascular risk factors to minimize their overall risk. These patients, therefore, require education in an ongoing fashion about the importance of maintaining a healthy diet, a healthy weight, the need for exercise, and the need to control those comorbid conditions Dr. Cortes mentioned such as hypertension, hyperlipidemia, and diabetes that impact their overall cardiovascular risk. Over the course of their treatment, providers should continue to monitor for these conditions as they could arise throughout the patient's ongoing treatment. Other conditions that can alter the selection of an appropriate TKI or potentially require increased monitoring include pancreatitis that can

be seen with nilotinib (Tasigna®) and ponatinib (Iclusig®) therapy and, ergo, might impact patients who have a history of either pancreatitis or alcoholism.

Now, nilotinib (Tasigna®) has also been associated with increased risk for hyperglycemia. However, there was a review of patients on frontline nilotinib (Tasigna®) therapy who have diabetes, and this did not show any increase in clinically relevant parameters such as hemoglobin A1C. Therefore, for this sort of drug-disease interaction, this may just require increased awareness and monitoring.

For dasatinib (Sprycel®), patients with underlying lung disease such as COPD may not be the best candidate due to increased risk of pulmonary arterial hypertension and pleural effusions as Dr. Cortes mentioned earlier, provided that the patient does have other TKI options. Now, of course, these are just some of the conditions to consider when a provider is reviewing a patient to select a TKI therapy; and notably, as again, patients are treated for potentially lifelong, in most patients, we must evaluate these patients over time for these new comorbidities and new concomitant medications as these can change and have new or dropped interactions, either with disease states or drugs over time.



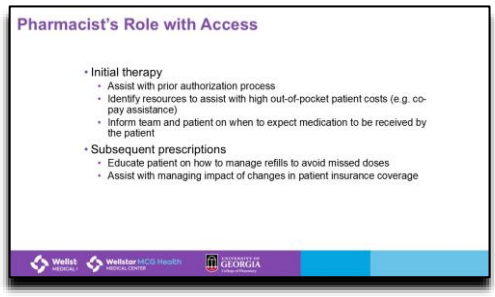
Slide 59: Medication Access

Moving on now to talk about medication access. These targeted oral therapies are unique entities, for which the cost of research and development is substantial; and that's reflected in the high cost of these products. Since oral therapies fall under a patient's prescription drug benefits, the out-of-pocket cost can be challenging to predict; but it's frequently very significant for patients and is known to be related to the patient's outcomes.

For example, there was one retrospective review of insurance claims and prescription refills and cost sharing information for over 1,500 patients with CML between 2002 and 2011. The primary outcome of that review was to look at TKI discontinuation and nonadherence within the first 180 days of initiating their therapy.
Discontinuation was defined as a break in therapy where there was a lack of refills resulting in 60 days or more without the medication, and adherence was defined as having a sufficient supply to cover more than 80% of the days during that 180-day assessment period.

The authors evaluated copay amounts by the patient as well as total monthly out-of-pocket expenses for the patient on the health plan. They found that patients with the higher out-of-pocket costs were 70% more likely to discontinue and 42% more likely to be nonadherent to their TKI therapy. They also noted that the mean monthly total expenditures were nearly doubled from 2002 to 2011, showing the increasing trend in

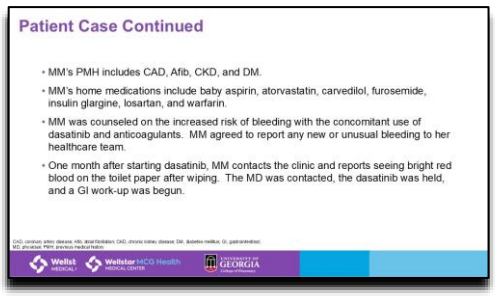
higher and rising healthcare costs, a topic which has been widely discussed in recent years and a trend that does not seem to be reversing at this time.



Slide 60: Pharmacist's Role with Access

So, pharmacists can play an integral role in ensuring patients have access to these high-cost medications. Pharmacists who work in an oncology clinic are frequently involved in the prior authorization process, serving as a contact person, assisting with providing appropriate documentation to the healthcare plan, and writing any letters of appeal or medical necessity when needed.

Once the prescription is successfully processed, there may be a high copay as we just discussed, and this can require the pharmacist to help the patient and their caregivers in finding and utilizing any resources available to offset these high costs. For subsequent prescriptions, the pharmacist can work with the patient to determine how best to ensure they get their refills on time to avoid missed doses. This may include utilizing automatic refills with options through their pharmacy, setting certain reminders, or using apps. Patients are on these therapies long term if not lifelong and, of course, patients' insurance companies and plans can change; and this may necessitate redoing some of these steps throughout the course of a patient's treatment.

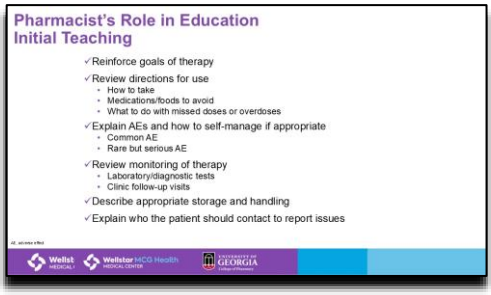


Slide 61: Patient Case Continued

Now, let's get back to our patient case for a moment. So, we see that MM has a medical history, including coronary artery disease, atrial fibrillation, chronic kidney disease, and diabetes for which she takes a baby aspirin, atorvastatin (Lipitor®), carvedilol (Coreg®), furosemide (Lasix®), insulin glargine (Lantus® SoloStar®), losartan (Cozaar®), and warfarin (Coumadin®). After reviewing the patient's information, these comorbidities and concomitant medications, the pharmacist would identify that there is a moderate interaction between her baby aspirin and warfarin (Coumadin®) with the planned new dasatinib (Sprycel®) therapy that could lead to an increased risk in bleeding.

This information could be relayed back to the oncologist for consideration, and in this case they want to proceed with the therapy and ask the pharmacist to give the patient some additional education so the patient can be counseled on this increased risk and be informed to report promptly any increase, new, or unusual bleeding. We see that for this patient, one month after starting dasatinib (Sprycel®), they do call the clinic and report seeing bright red blood on the tissue paper after wiping. So the oncologist being contacted

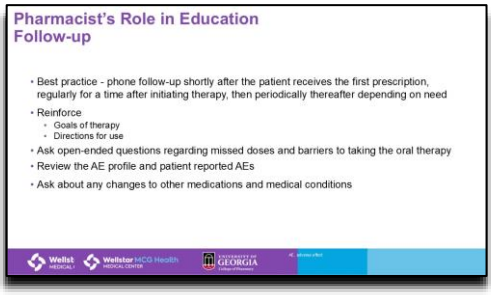
with this information has the patient hold the dasatinib (Sprycel®) therapy and start a GI workup. And again, we'll come back to MM in a moment.



Slide 62: Pharmacist's Role in Education Initial Teaching

So, as with any condition or medication, a pharmacist can play a central role in educating patients and caregivers on these therapies. When a patient starts a new oral chemotherapeutic agent, there are several areas that are very important for the pharmacist to review with the patient. First, it's important to reinforce the goals of treatment. These were already discussed by the patients' oncologist. However, having clear goals and ensuring patient understanding is critical to improve adherence and, as we've discussed, this is important for optimal outcomes.

Next, it's important for the patient to understand exactly how to take a medication correctly. An oral therapy, obviously, they're going to swallow the tablet or capsule. However, the patient understanding any interactions or timing with food or timing apart from other concomitant medications should be discussed in detail so the patient can take it correctly to benefit the most from the therapy. Lastly, the pharmacist should discuss with the patient what to do in case of a missed dose and any storage and safe handling instructions for these oral chemotherapeutic products. The patient should be informed about common as well as rare but potentially severe side effects to the agent, and my colleague will be speaking about some of these TKI side effects and how they will be managed shortly. In the case of our patient, she was educated about the potential increased risk of bleeding and did promptly contact the clinic when she experienced this as she was instructed to do so. Finally, when doing education with a patient, it's always important to confirm understanding; and it's best to do this in a teach-back method, and any further discussion can occur at that point if necessary to reinforce or correct any information.

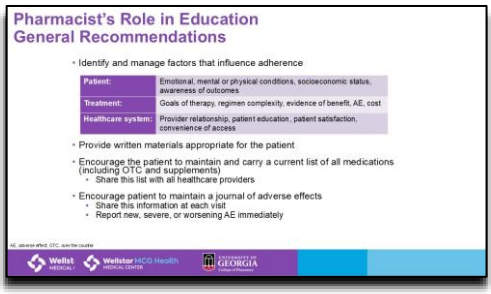


Slide 63: Pharmacist's Role in Education Follow-up

As we discussed earlier, one of the few but important challenges with oral cancer therapies is monitoring for adherence. ASCO and ONS have standards for safe handling, administration, and management of oral chemotherapy; and they recommend that you have a formal process for assessing adherence with these agents. Thus, after an initial prescription is provided to a patient, many oncology clinics are going to meet this standard through phone call follow-up visits.

The purpose of these calls is to confirm that the patient did receive the medication, has started it, and to determine if they're experiencing any problems such as financial barriers. Further, these phone calls should rereview some of the key initial education points as well as inquire about any side effects the patient may be experiencing thus far.
The rereview should cover the directions for administration as we just discussed, how best to take the medication, the potential side effects to monitor for as well. It's important that at subsequent either in-person or phone clinic visits that the patient's medication history and list of medications is updated in the chart and are read to identify any new or changed interactions that may warrant either provider awareness or potential increased monitoring or education to the patient.

As with any follow-up, it's important to ask some open-ended questions and identify any issues. So, ask the patient how they're taking their medication, specifically probing about timing, either related to food or other medications as is relevant to whichever TKI the patient is prescribed. Also, have the patient tell you how many missed doses of the medication they've had, rather than asking a yes/no close-ended question in order to fully determine any adherence barriers they may be having. Also, you can inquire to the patient about financial concerns which may impact their ability to get their refills on time, which, as we've discussed, is very important in order to achieve optimal outcomes.



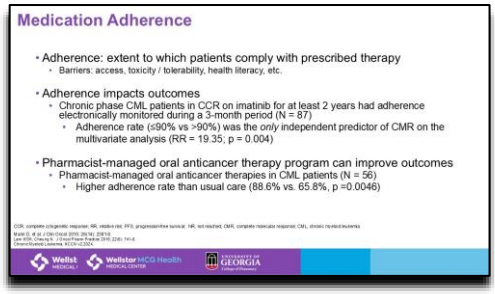
Slide 64: Pharmacist's Role in Education General Recommendations

So, one of the most important tasks a pharmacist can take on during these interactions with patients is identifying and managing any factors that are impacting their adherence. Generally, these fall into three categories, either patient-related, treatment-related, or healthcare system-related. Examples of these are listed on the slide, and we've already spoken about many of them, including awareness of outcomes, cost, and education.
So verbal education is obviously very important, but this should be supplemented with written documentation that the patient can reference at a later time if needed. This written information and those follow-up phone calls we discussed can ensure the patient truly understands all of the information provided and knows when to act.

As the patients tend to be middle-aged or older-aged adults, we have to consider that they often have the comorbidities that necessitate using multiple healthcare providers and potentially multiple healthcare systems. They can also have changes in their medication regimen for those comorbidities over time. So, as I mentioned, we should instruct patients to always have a complete medication list; and they should give that to all providers, not just their oncologist at each healthcare encounter for any problem. We should also encourage our patients to keep some sort of journal or log of their side effects or any problems they're having with their oral oncolytics so they can bring these concerns and

issues to their oncologist at each either phone call or in-person follow-up visit for discussion.

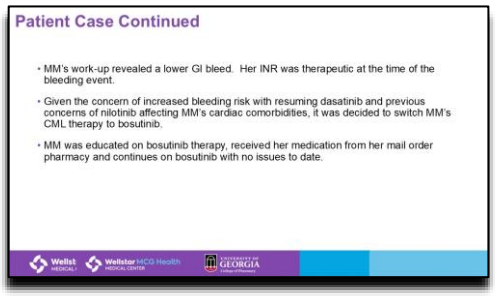
Considering these therapies are long term, if not lifelong for most patients, a persistent minor side effect like diarrhea or fatigue can be just as much of a barrier to optimal adherence as a major but rare side effect can be.



Slide 65: Medication Adherence

So, we've been talking about adherence for a number of slides and why it's important in this population. The patient's ability to comply with the prescribed therapy has been shown to affect outcomes. There was one paper that looked at the impact of adherence with TKIs and outcomes. They reviewed a group of patients with CML who were in a complete cytogenetic response for at least the two years. These patients had their adherence to their therapy monitored via a microelectronic monitoring device on the cap of their prescription bottle for a three-month period.

The primary outcome was molecular response, and they found in this analysis that the only independent predictive factor of achieving that complete molecular response was adherence using a cutoff of 90%, meaning that if you were able to take 90% or more of your prescribed doses, you were more likely to achieve a molecular response.
And notably, there were no molecular responses reported in patients who had an adherence rate of less than 80%. There have also been some publications surrounding the outcomes of patients with oral oncolytics who received pharmacist-managed oral anticancer care. In one study, patients with CML specifically who received care that included the aid of a pharmacist did have higher adherence rates than usual care.

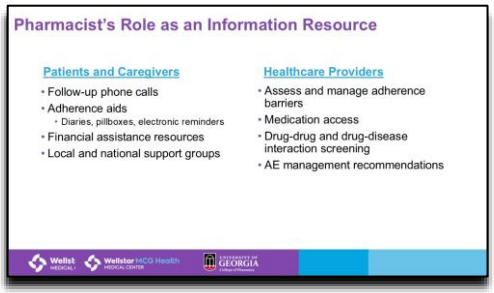


Slide 66: Patient Case Continued

Now, let's get back to our patient MM who, unfortunately, her workup did reveal a lower GI bleed. At the time of the bleeding event, her INR was within normal therapeutic range. So given the concurrent risk of bleeding with these medications, the oncologist determined to discontinue the dasatinib (Sprycel®) therapy.

Now recall this patient has already received imatinib (Gleevec®) and nilotinib (Tasigna®) previously. Thankfully, as Dr. Cortes mentioned, we have multiple agents FDA approved to treat chronic myeloid leukemia; so at this time she is now being able to be initiated on bosutinib (Bosulif®) therapy for which a new prescription is sent to her pharmacy,

medication education needs to be performed, and again, access to care process needs to be reinitiated to make sure she can achieve this medication.

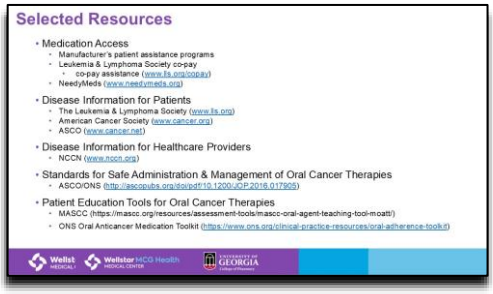


Side 67: Pharmacist's Role as an Information Resource

So, pharmacists may find themselves in a position where they can't provide face-to-face conversations with patients such as MM; but they can be supportive in other ways. As I mentioned, some clinics and even some healthcare plans by insurance companies may have programs established where the pharmacist can perform phone call visits in order to assure the patient can obtain the medication, be adherent, and isn't experiencing any difficulties, for example, with side effects.

So, a pharmacist, regardless of setting, can assist the patient also in overcoming adherence issues by giving them tools to work with for refills such as using pill boxes, app reminders, alert reminders, or using certain diaries. They can also impact a larger audience by providing talks such as these and leading discussions perhaps with local patient support groups to provide medication and disease information in that vein. Pharmacists can also help the healthcare providers in managing these patients by helping navigate the access to care that we've discussed, helping them identify and mitigate any barriers to adherence, and help them understand the drug information for each agent in order to optimally select patient-specific regimens based on patient-specific factors throughout the course of their treatment.

Screening for interactions can lead to recommendations for treatment, which may include increased patient education or monitoring needs. Further, the pharmacist can assist the healthcare team in recognizing and managing the side effects to these therapies that they may experience over the course of their treatment.



Slide 68: Selected Resources

Here's a list of some resources that pharmacists and the healthcare providers may find useful while managing patients with CML.

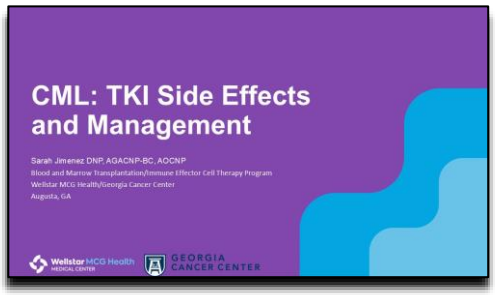
Slide 69: Summary

And in summary, our oral anticancer therapies are integral to the management of CML in achieving optimal outcomes. As Dr. Cortes discussed, this is a lifelong disease for most patients, and pharmacists and providers should recognize that this long-term treatment presents a huge challenge, primarily focused on adherence. And we know that adherence can impact achievement of our goals of care and, therefore, adherence should be discussed and addressed with a patient at every visit with the provider.

Pharmacists are just one of the many healthcare providers that can be involved in the care of these patients, and we are well poised to impact adherence. We can also assist with medication access, providing education to patients and caregivers, as well as serving as a drug information resource to the oncologist. This concludes my part of the presentation.

Slide 70: Thank You

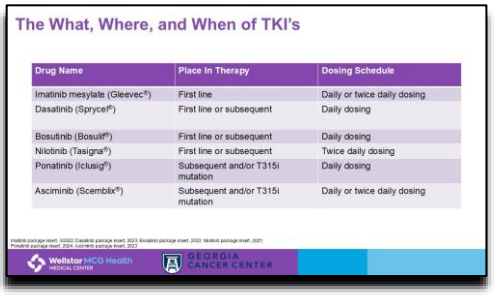
Lauren Berger: Lauren Berger: Thank you Dr. Cortes & Dr. Clemmons for your very clear and informative presentation.



Slide 71: CML: TKI Side Effects and Management

Lauren Berger: I am now pleased to introduce Advanced Practice Provider Sarah Jimenez. Dr. Jimenez is Lead Advanced Practice Provider for the Blood and Marrow Transplantation and Immune Effector Cell Therapy Program at Wellstar MCG Health/Georgia Cancer Center in Augusta, Ga. Dr. Jimenez?

Sarah Jimenez, DNP, AGACNP-BC, AOCNP: Hello, and thank you for participating in this educational discussion on CML and the management of side effects for tyrosine kinase inhibitors. My name is Sarah Jimenez, and I'm the lead advance practice provider for the Blood and Marrow Transplant Program at Wellstar MCG Health, Georgia Cancer Center in Augusta, Georgia.

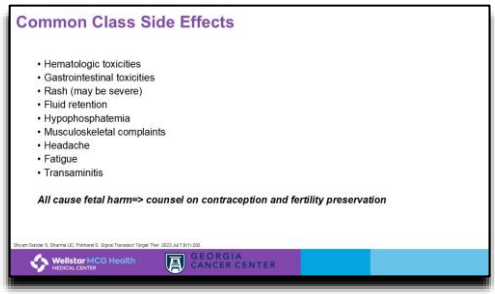


Slide 72: The What, Where, and When of TKI's

This slide is a brief overview of the commercially available tyrosine kinase inhibitors, their place in therapy, and dosing schedule. In 1999, Gleevec® (imatinib) became the first tyrosine kinase inhibitor on the block; and as you can see, nearly 25 years later, we now have six available medications in this class to offer patients with CML.

When a patient is diagnosed with CML, the physician will take into consideration the advantages and disadvantages of each tyrosine kinase inhibitor in terms of treatment response, disease risk, the patient's comorbidities, the prescription costs, and the use of second-generation TKIs based on the patient's background when determining the appropriate TKI for first-line treatment.

Imatinib (Gleevec®) is generally used as a first-line medication. However, dasatinib (Sprycel®), bosutinib (Bosulif®), and nilotinib (Tasigna®) can be used as first line or subsequent lines of therapy. Imatinib (Gleevec®) and asciminib (Scemblix®) are reserved for subsequent lines of therapy or for those patients who have T315i mutations.

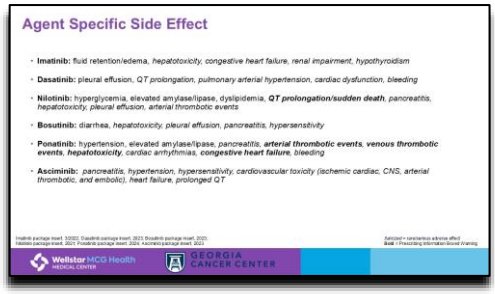


Slide 73: Common Class Side Effects

There are some common side effects that we can see across all tyrosine kinase inhibitors. As a class, the most common side effects include hematological malignancies; GI toxicity such as nausea, vomiting, diarrhea; rashes that can range from mild to severe; electrolyte abnormalities; musculoskeletal complaints such as arthralgias, myalgias, and cramping; headaches; fever; and liver dysfunction.

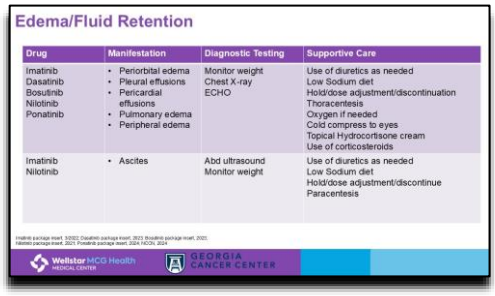
It is important that tyrosine kinase inhibitors are tetrogenic and can cause fetal harm. Patients should be counseled on contraception options while on treatment, and if the patient is young and of childbearing age potential, they should be referred to reproductive medicine for fertility preservation options.

Currently, young female patients who wish to become pregnant should work closely with their oncologist and obstetrician regarding timing of TKI discontinuation prior to conceiving, and will need to be monitored closely during pregnancy and off treatment.
For men taking imatinib (Gleevec®) or any second-generation TKIs such as bosutinib (Bosulif®), dasatinib (Sprycel®), or nilotinib (Tasigna®), there is no increased risk of congenital abnormalities in the offspring. Thus, men planning to father children do not need to discontinue treatment.



Slide 74: Agent Specific Side Effect

There are some agent-specific side effects that providers need to be aware of and take into consideration, the patient's comorbidities prior to selecting which TKI they will use for patients. Some of these side effects are mild. However, others can be life-threatening. I've put in bold font the side effects that come as a black box warning. For instance, nilotinib (Tasigna®) has a black box warning for QT prolongation and sudden death; and ponatinib (Iclusig®) has a black box warning for arterial and venous thrombotic events, heart failure, and liver failure. Patients will need to be monitored closely for these complications while on treatment. And if the patient has a prior history of these health issues, then alternate regimens should be considered. In the following slides, we're going to take a deeper dive into these side effects and the recommended management.



Slide 75: Edema/Fluid Retention

The following slides, we're going to discuss common side effects, diagnostic testing that may be ordered, and supportive care recommendations. I've tried to arrange these slides in such a way that it makes it easy to reference them in the future. At any time a patient presents with symptoms, it's very easy to blame the drug or even their disease for the symptoms that they're having. However, it's really important that we rule out other causes that may be causing the symptoms, and this will help us treat our, guide our treatment decisions.

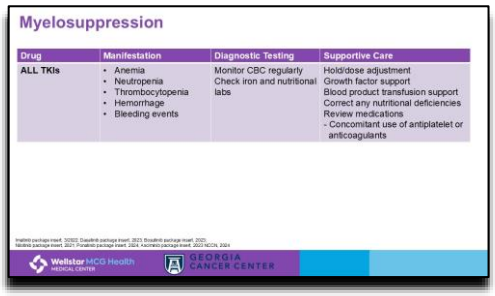
Fluid retention and edema is commonly seen. This may manifest as periorbital edema, pleural or pericardial effusions, peripheral edema, and ascites. Patients' weight should be monitored at each clinic visit; and a healthcare provider may order tests such as a chest x-ray, echocardiogram, or abdominal ultrasound to evaluate the patient's symptoms. Fluid retention and peripheral edema can be treated with diuretics as needed. A low sodium diet can also help.

It's important to remember that if we are putting patients on diuretics, that we need to monitor their potassium levels and their renal function very closely. Periorbital edema is usually worse in the morning and can improve throughout the day. And for this, cold compresses on the eyes or Anusol™ (hydrocortisone) can help reduce the swelling. Patients who have pleural effusions are going to have decreased breath sounds in the bases of their lungs when you listen to them, and they may complain of a dry cough. Diuretics and steroids may be useful in treating pleural effusions and ascites. And if the

pleural effusions are large enough, a thoracentesis may be needed in order to drain the fluid to give the patient relief.

It's important to send this fluid for diagnostic testing to see if the fluid is malignant in nature or possibly an underlying infection. This is just on a personal note. I did have a patient who has CML and a history of breast cancer, and she was being treated with dasatinib (Sprycel®), and she had developed pleural effusions. So, the assumption was that the dasatinib (Sprycel®) was the cause of her effusions. However, after I ordered a diagnostic thoracentesis, the fluid was actually related to metastatic breast cancer. So, that's where I just put the caveat that is very important that we know what the underlying cause of the symptom is. Otherwise, we may change treatment prematurely.

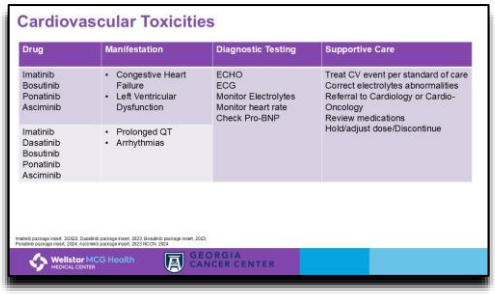
To those who develop ascites, you may have to send them for a paracentesis to remove the fluid from their abdomen. And again, it'll be important to send that fluid for diagnostic testing. And if the patients have severe symptoms that can't be managed, then treatment will be held, their dose may need to be adjusted or discontinued altogether.



Slide 76: Myelosuppression

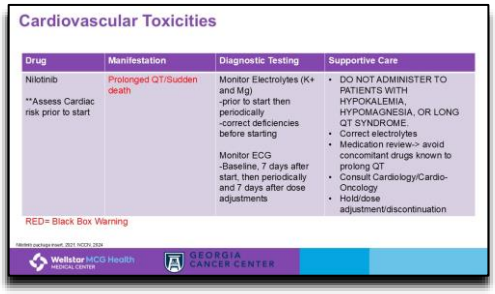
All tyrosine kinase inhibitors can cause myelosuppression, mostly anemias, neutropenia, and thrombocytopenia. CBCs should be monitored regularly, and if the patient does develop cytopenias, I would recommend checking their iron in nutritional studies. Many patients have or will develop nutritional deficiencies, which can contribute to their low blood counts.

If the cytopenias are related to nutritional deficiencies, they generally improve once the patient is placed on the appropriate supplements. However, if the cytopenias are not diet related, then the patient can be supported with growth factors and blood products. Their tyrosine kinase inhibitor may also need to be held until the cytopenias improve or their dose may need to be adjusted. For patients with thrombocytopenia, it is also important that we review the patient's medications to ensure they're not on any concomitant antiplatelet or anticoagulants. And if so, those medications should be held until the platelet count improves.



Slide 77: Cardiovascular Toxicities

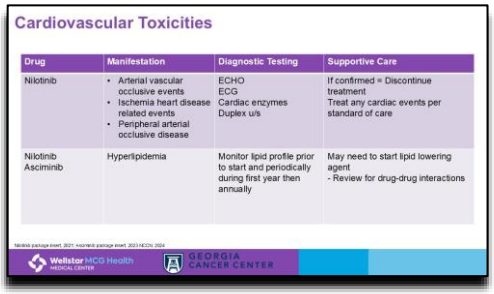
Cardiovascular toxicities such as congestive heart failure, prolonged QT, and arrhythmias can occur. If a patient presents with cardiac symptoms, the provider may order an echo, an EKG, a proBNP, and check their electrolytes. Any cardiac event should be treated per the standard of care and referral to cardiology or cardio-oncology is recommended. If the patient does have electrolyte abnormalities, it's important for us to correct these as they may be contributing to any of their arrhythmias. And if the patient has prolonged QT, it's also important to review their medications for any concomitant use of medications that could be contributing to their prolonged QT, such as azoles, like fluconazole (Diflucan®). And depending on the circumstance and severity of the tyrosine kinase inhibitor, it may need to be held. The dose may need to be adjusted or discontinued.



Slide 78: Cardiovascular Toxicities

Nilotinib (Tasigna®) comes with a black box warning for prolonged QT and sudden death. It's important to assess patients' risks before starting nilotinib (Tasigna®). And if the patient has electrolyte abnormalities such as hypokalemia or hypomagnesia, or have a history of long QT syndrome, then nilotinib (Tasigna®) should not be administered.

Any electrolyte abnormalities should be corrected prior to starting, and a CMP should be monitored closely while they're on treatment. Also, an EKG should be done prior to starting therapy, seven days after they start therapy, and then periodically thereafter or seven days after any dose adjustment. Again, a close review of the patients' medication should be done to ensure they're not taking any other medications that could cause prolonged QT; and the patient should be referred to cardio-oncology or cardiology for further work-up and recommendations and discontinuing of the medication may be warranted.

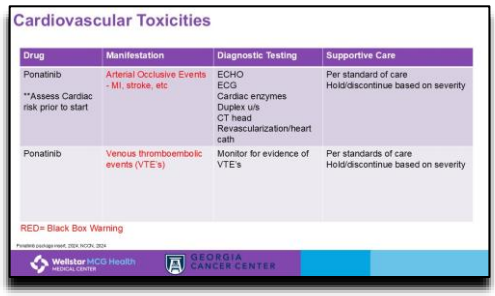


Slide 79: Cardiovascular Toxicities

Nilotinib (Tasigna®) can also cause venous occlusive events, ischemic heart disease, and peripheral artery occlusive disease. Diagnostic testing such as an echo, EKG, cardiac enzymes, and duplex may be ordered. And any cardiac event should be treated per the standard of care. If these events are confirmed in

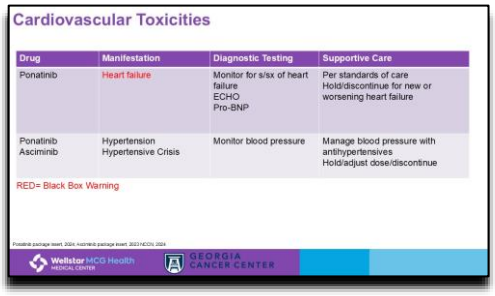
the patient, then nilotinib (Tasigna®) should be discontinued.

Nilotinib (Tasigna®) and asciminib (Scemblix®) can cause hyperlipidemia. A lipid profile should be checked prior to starting these medications and then periodically, generally about every six months during the first year and then annually thereafter. Patients may require a lipid lowering agent. However, it needs to be taken into account which drug to use due to drug-drug interactions; and our pharmacists are very helpful in assisting us selecting the right medication.



Slide 80: Cardiovascular Toxicities

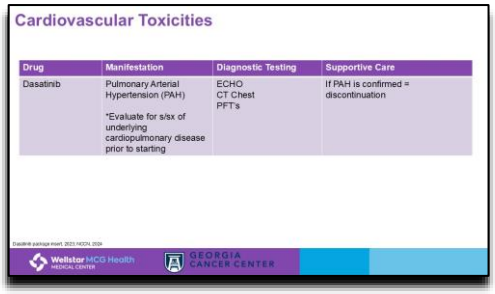
Ponatinib (Iclusig®) carries a black box warning for arterial occlusive events such as myocardial infarctions and strokes as well as venous thromboembolic events. Providers need to assess the patient's risk prior to starting any of these therapies. And if the patient does develop complications while on ponatinib (Iclusig®), then it would need to be held or potentially discontinued, depending on the severity. And the patient should be treated per the standard of care.



Slide 81: Cardiovascular Toxicities

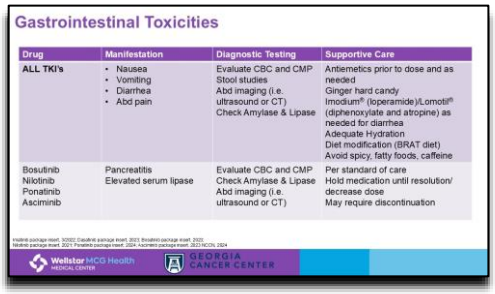
Ponatinib (Iclusig®) also carries a black box warning for heart failure. Patients should be monitored for signs and symptoms of heart failure during each clinic visit. And if they develop symptoms, an echo or proBNP should be ordered. Heart failure should be treated per the standard of care, and ponatinib (Iclusig®) should be held and maybe require discontinuation.

Ponatinib (Iclusig®) and asciminib (Scemblix®) can lead to patients developing hypertension or hypertensive crisis. Their blood pressure should be monitored at their visits, and if they develop hypertension, antihypertensive medications should be ordered accordingly. Depending on the severity, therapy may need to be held. Their dose may need to be adjusted or discontinued.



Slide 82: Cardiovascular Toxicities

Pulmonary artery hypertension can also be seen in patients who are taking dasatinib (Sprycel®). Providers should evaluate for signs and symptoms of cardiopulmonary disease prior to starting dasatinib (Sprycel®). And if they develop symptoms, they may order an echo, a CT of the chest, or pulmonary function tests. If the diagnosis of pulmonary artery hypertension is confirmed, then dasatinib (Sprycel®) should be discontinued. And I highly recommend that patients be referred to cardiology or cardio-oncology if they develop any cardiovascular side effects; and the provider needs to work closely with them in order to manage the patients while on tyrosine kinase inhibitors.



Slide 83: Gastrointestinal Toxicities

Now we're going to move onto the gastrointestinal toxicities. All TKIs can cause nausea, vomiting, and abdominal diarrhea, and abdominal pain. Pancreatitis can also be seen in patients taking bosutinib (Bosulif®), nilotinib (Tasigna®), ponatinib (Iclusig®), and asciminib (Scemblix®). If patients present with GI symptoms, providers will likely check a CBC, a CMP, and check stool studies to look for infections; and they'll check an amylase and lipase to look for pancreatitis and could potentially order abdominal imaging.

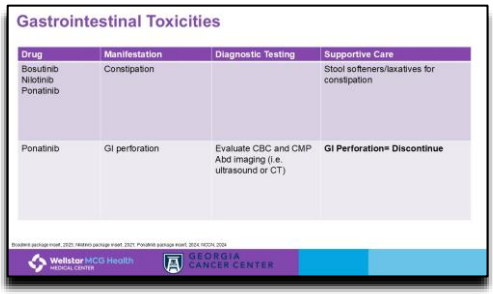
For patients with nausea and vomiting, the patients can take antiemetics about 30 minutes prior to their TKI as needed. Ginger hard candies may also be helpful in managing nausea, and generally the nausea will improve over time. Diet modifications such as instituting the BRAT diet and avoiding spicy or fatty foods and caffeine may be needed. And referring the patient to the dietitian may also be helpful as it can help the patient learn how to choose better dietary choices.

Dyspepsia and reflux can also occur, and we, but we need to be mindful that when taking TKIs that certain TKIs we have to avoid antacid, H2 blockers, and PPIs. And we're going to discuss that a little further a little later on.

Diarrhea is also common in these patients. Patients who are on bosutinib (Bosulif®) will develop diarrhea pretty quickly; and if this occurs, it will occur pretty soon after taking their dose. When starting patients on bosutinib (Bosulif®), I usually tell them to stay home or stay close to home when they first start the bosutinib (Bosulif®) since the diarrhea is usually pretty rapid onset. And they can take Imodium® (loperamide) or Lomotil® (diphenoxylate and atropine), and this can be taken as needed for diarrhea, and they need to drink plenty of fluids to ensure adequate hydration. Probiotics can also be used to help

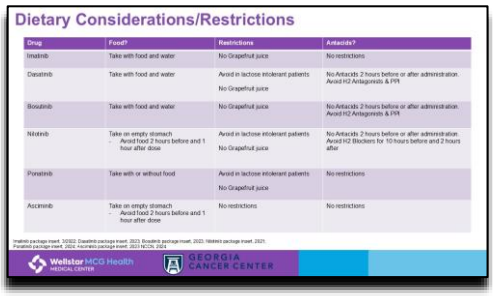
restore the gut flora, and then generally this diarrhea will improve over the next few months.

If a patient develops pancreatitis, they should be treated per the standard of care; and the tyrosine kinase inhibitor will be held until their symptoms resolve. However, dose adjustment or discontinuation may be required.



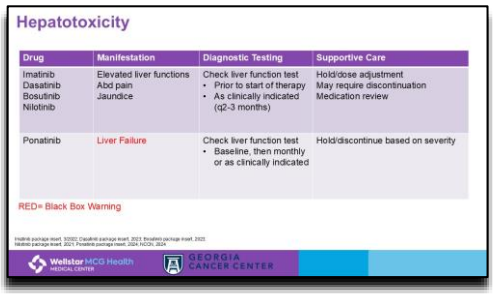
Slide 84: Gastrointestinal Toxicities

Some patients may experience constipation, and this can be managed with stool softeners or laxatives. There's even a Smooth Move® tea that patients can use, and GI perforation has also been seen in patients who take ponatinib (Iclusig®). And if this occurs, ponatinib (Iclusig®) should be discontinued.



Slide 85: Dietary Considerations/Restrictions

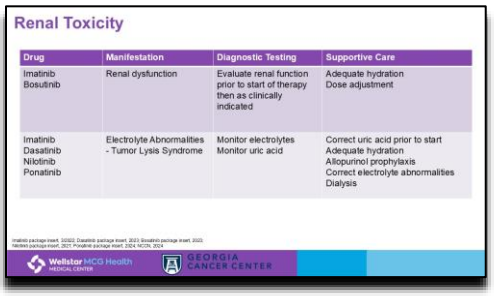
The dietary considerations or restrictions. There's some variations between the different types of tyrosine kinase inhibitors regarding this. Imatinib (Gleevec®), dasatinib (Sprycel®), bosutinib (Bosulif®), and ponatinib (Iclusig®) can all be taken with food and water. However, the other ones, nilotinib (Tasigna®) and asciminib (Scemblix®) need to be taken on an empty stomach. Dasatinib (Sprycel®), nilotinib (Tasigna®), and ponatinib (Iclusig®) should be avoided in patients who have lactose intolerant because they do contain lactose. Grapefruit should be avoided in all tyrosine kinase inhibitors as it does increase the effects of the medication, with the exception of asciminib (Scemblix®). And then antacids, H2 blockers, and PPIs can also be an issue with patients who are on dasatinib (Sprycel®), bosutinib (Bosulif®), or nilotinib (Tasigna®) as they do reduce their absorption. Antacids should be avoided for two hours before or after administration, and H2 blockers and PPIs should be avoided.



Slide 86: Hepatotoxicity

Hepatotoxicity can be seen in patients who are taking imatinib (Gleevec®), dasatinib (Sprycel®), bosutinib (Bosulif®), and nilotinib (Tasigna®). Ponatinib (Iclusig®) does have a black box warning for liver failure. Liver function should be checked prior to starting therapy and then typically every two to three months thereafter. Patients may present with abdominal pain or appear jaundiced and may have elevated liver functions. If this occurs, therapy should be held until improvement, and it may require a dose adjustment or

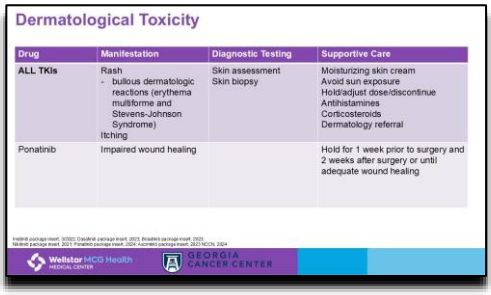
discontinuation. And we need to be careful what other medications they are also on, to be done to evaluate if there's other medications that could be causing hepatotoxicity as well.



Slide 87: Renal Toxicity

Imatinib (Gleevec®) and bosutinib (Bosulif®) can cause renal dysfunction, and as such renal function should be evaluated prior to starting treatment and then periodically thereafter. It's important that patients maintain adequate hydration, and if they have renal impairment, a dose adjustment may be needed.

Tumor lysis syndrome can also be seen, and it's important that we monitor the patient's electrolytes, renal function, and uric acid when starting treatment. And allopurinol prophylaxis may be given at the start of treatment to prevent TLS. We need to ensure the patient is adequately hydrated and any electrolyte abnormalities are promptly corrected. And in severe cases, the patient may require hemodialysis.

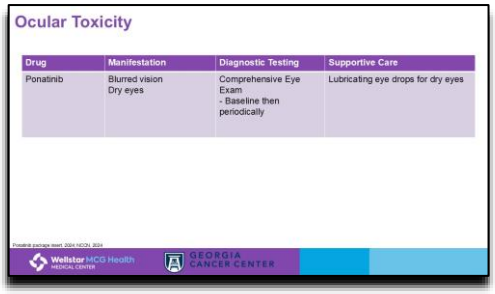


Slide 88: Dermatological Toxicity

Rashes and itching can be seen with all tyrosine kinase inhibitors. However, it can be more severe in patients taking bosutinib (Bosulif®). Cases of Stevens-Johnson Syndrome have been reported, and severe cases of rashes may require hospitalization. Careful skin assessment should be performed at clinic visits; and if needed, the patient should be referred to dermatology and a skin biopsy may be performed.

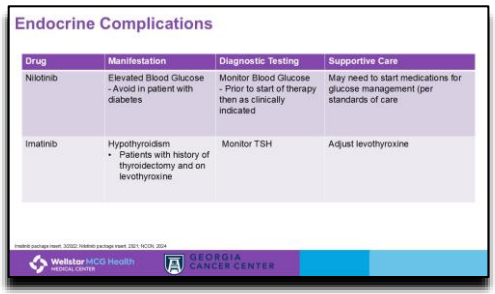
Moisturizers and mild exfoliants with hydraulic acid and salicylic acid are helpful for mild-to-moderate rashes, as well as oral antihistamines. Patients should avoid sun exposure and wear protective clothing and sunscreen. And depending on the severity, corticosteroids may be needed; and tyrosine kinases may need to be held, adjusted, or discontinued.

And then for ponatinib (Iclusig®), impaired wound healing can be seen. So, this medication should be held for one week prior to any surgery and then two weeks after the surgery or until the wound is healed.



Slide 89: Ocular Toxicity

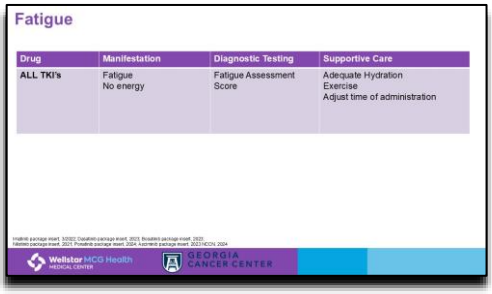
Patients on ponatinib (Iclusig®) can develop ocular complaints such as blurred vision or dry eyes, and a comprehensive eye exam should be done at baseline and then periodically thereafter prior to starting, when they start ponatinib (Iclusig®). And if they have dry eyes, they can use lubricating eye drops, which can be helpful.



Slide 90: Endocrine Complications

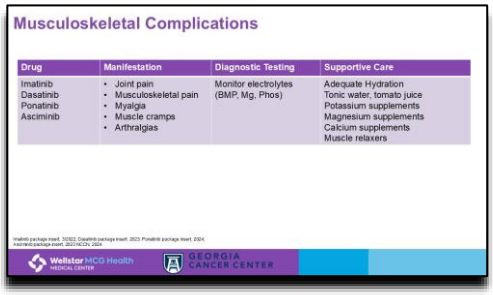
And then endocrine disorders can be seen in patients taking nilotinib (Tasigna®) or imatinib (Gleevec®). Nilotinib (Tasigna®) should be avoided in patients who have preexisting diabetes as it can cause elevated blood glucose levels. And the blood glucose levels should be monitored closely. And if they do develop hyperglycemia, medications may need to be started for glucose management.

Imatinib (Gleevec®) can also cause hyperthyroidism in patients who already have a history of thyroidectomy or, and on levothyroxine (Synthroid®). For these patients, TSA should be monitored closely, and levothyroxine (Synthroid®) may require dose adjustments.



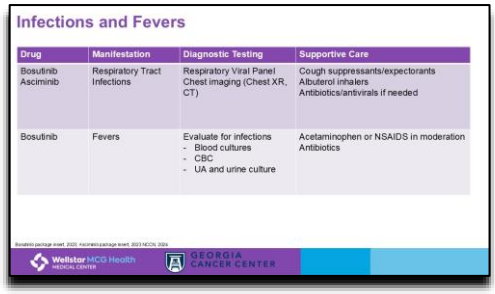
Slide 91: Fatigue

Fatigue is a very common side effect that patients are going to complain of. Fatigue Assessment Score should be done at each clinic visit, and the patient should be encouraged to exercise and drink plenty of fluids. Sometimes taking the medication at night can help with the daytime fatigue since they're sleeping through the majority of the side effects.



Slide 92: Musculoskeletal Complications

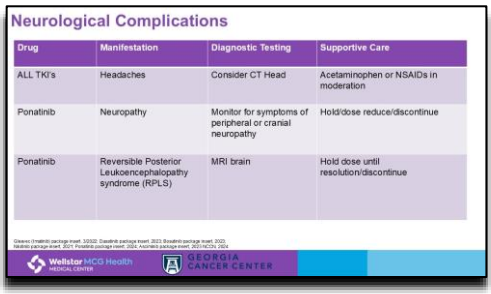
Musculoskeletal complaints such as joint pain, myalgias, arthralgias, and muscle cramps can occur. It's important to ensure that patients are drinking plenty of fluids. Drinking something like tonic water, pickle juice, and tomato juice can also help. And if the patient has electrolyte imbalances that are contributing to their symptoms, then potassium, magnesium, and calcium supplements may be used. Sometimes we also prescribe muscle relaxers to help the patient.



Slide 93: Infections and Fevers

Patients who are taking bosutinib (Bosulif®) and asciminib (Scemblix®) are a little more prone to developing respiratory tract infections. And if this occurs, then a respiratory viral panel should be ordered and chest imaging can be done. These infections can be treated with cough suppressants and expectorants, albuterol inhaler, and antibiotics and antiviral medications if needed.

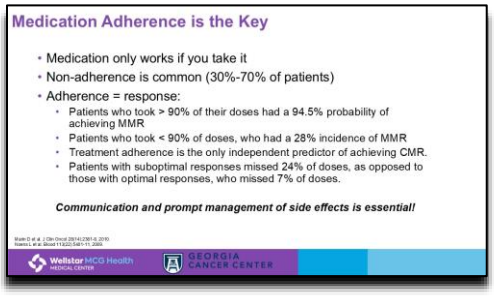
Fevers can also be seen in patients on bosutinib (Bosulif®), but, and it's important that we assess for signs and symptoms of infection any time a patient has a fever, thus an infectious workup should be done. An infection should be treated accordingly. And it's okay for the patient to take Tylenol® (acetaminophen) or NSAIDs in moderation for the fevers.



Slide 94: Neurological Complications

Neurological complications such as headaches, neuropathies, and reversible posterior leukoencephalopathy syndrome have occurred. Headaches can be seen with all TKIs, but for patients who have persistent headaches that aren't getting better, we may want to order imaging of their head with a CT. Tylenol® (acetaminophen) and NSAIDs are okay to use in moderation for their headaches, but generally these headaches will improve over the first few months.

Ponatinib (Iclusig®) can cause neuropathies and reversible posterior leukoencephalopathy syndrome. It's important to monitor patients for signs of neuropathy during their clinic visit, and depending on the severity, we may require the ponatinib (Iclusig®) to be held, the dose reduced, or discontinued. Reversible posterior encephalopathy syndrome, the patients are going to present with headaches, confusion, seizure, and may have weakness. And if this occurs, an MRI of the brain will be done to confirm the diagnosis. And if it is confirmed, then the drug needs to be held until resolution and may need to be discontinued.

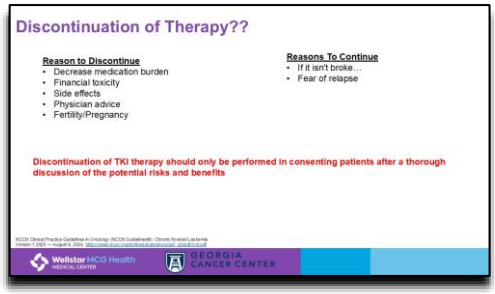


Slide 95: Medication Adherence is the Key

We have learned that tyrosine kinase inhibitors come with some baggage. Because of the side effects, patients may not always take their medications as prescribed and even miss doses. Medication nonadherence is common and has been reported in 30% to 70% of patients. We know that these

medications work, but they only work if patients take them. Studies done by David Marin and the ADAGIO trial by Lucien Noens had shown that patients who took more than 90% of their doses had almost a 95% probability of achieving a molecular remission. However, patients who missed more doses had a lower incidence of achieving a molecular remission.

Because of this, the communication with the patient and prompt, effective management of side effects is essential. Patients should be encouraged and empowered to communicate with their treatment team between office visits if they're experiencing side effects. I always tell my patients that if they're having issues and having side effects, I want to know now and not when they come back in three months to see me. I can't help them if they don't tell me. So, this is where we really need to utilize our triage nurses, our nurse clinicians and navigators who can really make an impact as they can promptly respond to patients and communicate strategies to help with side effects that the patient may be experiencing which will, in turn, promote medication adherence.

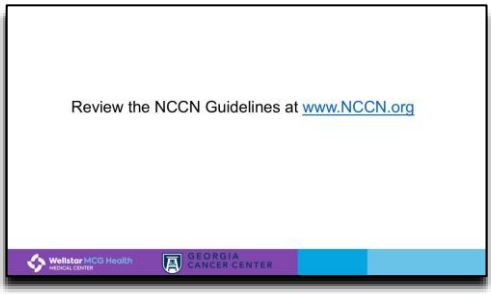


Slide 96: Discontinuation of Therapy??

The discontinuation therapy? So, can we ever stop treatment? Discontinuation of therapy can now be considered for patients who achieve and maintain a stable deep molecular response for at least two years and have been on tyrosine kinase inhibitors for at least three years are considered good candidates.

But this should only be done under medical supervision. Reasons why people may want to discontinue is that they want to decrease their medication burden, maybe there's financial toxicity involved, maybe they're, having a lot of side effects of treatment. Maybe the physician thinks it's a good idea, or maybe the patient's considering getting pregnant.

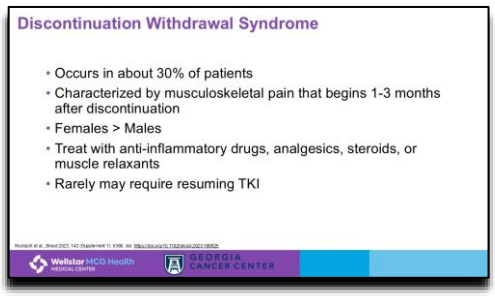
However, discontinuation can be very stressful for patients as they may have a fear of relapse. So, discontinuation should only be performed after careful discussion of the risks and benefits with the patient and then after their consent.



Slide 97: NCCN Guidelines

The NCCN guidelines have actually published guidelines for discontinuation of TKIs. TKIs should only be discontinued in patients who are adults older than age 18, those who are in chronic phase with no prior history of accelerated or blast phase, have been on TKIs for at least three years, and have an MR4 for at least two years or more and have access to PCR testing capable of detecting an MR4.5 and getting results back within two weeks.

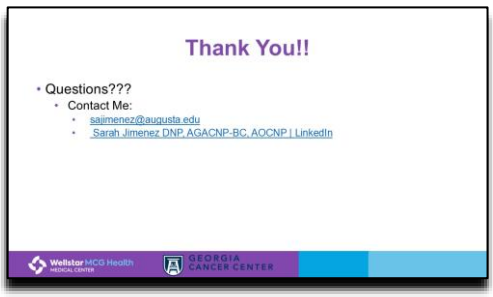
Once the TKI is discontinued, BCR-ABL should be monitored every one to two months for the first six months, then bimonthly for another six months, and then quarterly thereafter. At any time the patient loses their molecular response, then the TKI should be promptly resumed, and PCR should be monitored monthly until they're back into an MMR and then every three months indefinitely.



Slide 98: Discontinuation Withdrawal Syndrome

And then when we do discontinue patients from their TKIs, there is a syndrome called discontinuation withdrawal syndrome, and this can occur in about 30% of patients and usually present with musculoskeletal symptoms usually in that first one to three months after discontinuation.

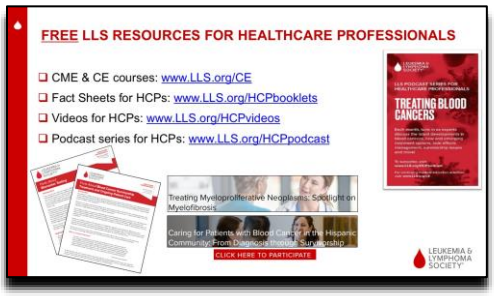
This occurs most frequently in females and can be treated with anti-inflammatory medications, analgesics, steroids, and muscle relaxers. Rarely the TKI may need to be resumed if the symptoms don't improve or resolve.



Slide 99: Thank You

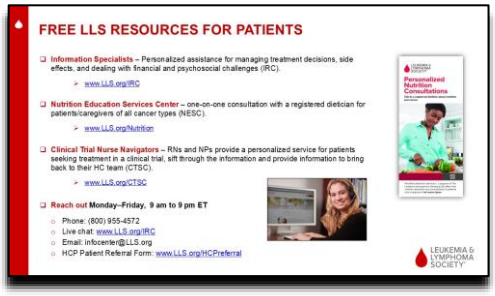
And thank you very much for listening to this lecture, and if you have any questions, I have listed my contact information on this slide. Thank you.

Thank you, Dr. Jimenez, for your informative presentation.



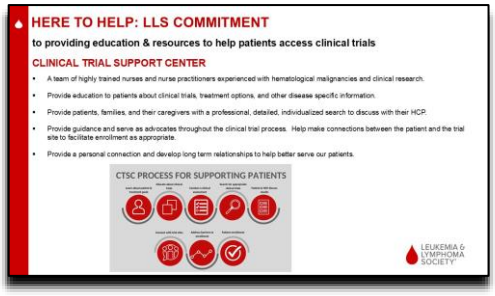
Slide 100: Free LLS Resources for Healthcare Professionals

I am now pleased to share free resources for you and your patients. The Leukemia & Lymphoma Society offers free CE and CME online webinars such as this one; in-person regional programs and a podcast channel for healthcare professionals, where you can listen to discussions on treatment, side-effect management and more, including strategies to support you and your patients. New and interesting topics are added every few weeks. Access these as well as videos and fact sheets for HCPs @ www.LLS.org/CE.



Slide 101: Free LLS Resources for Patients

LLS Information Specialists are highly trained Oncology Social Workers and Nurses who provide accurate, up-to-date disease, treatment and support information, including financial. Patients can contact them directly, or you can complete a referral form. Specialists can also help you order free copies of booklets to give to your patients. LLS offers free nutrition consultation to patients and caregivers with any type of cancer diagnosis in a 30-minute phone call w/one of our registered dietitians. Contact them using the link or phone number here to refer a patient. They work one on one with patients, via telephone, to provide user friendly information, do a nursing assessment to provide personalized information, help find appropriate clinical trials, assist them throughout the clinical trial process and provide info for the patient to bring back to their healthcare professional.



Slide 102: Here to Help: LLS commitment

The goal is not to enroll every patient into a trial, rather to increase opportunities for participation by facilitating informed decision making and minimizing logistical barriers for the patient. They work in collaboration with the patient's healthcare team to decide if a clinical trial is right for them. Ultimately, they educate, support, and empower patients to be active participants in, and have control over their treatment decisions. This is unique service from LLS. I hope you will consider all of these specialists as an extension of your team.

Slide 103: Free LLS Resources for Patients and Caregivers

LLS offers blood cancer disease specific information and support resources for patients and caregivers, including telephone and web education programs, videos, podcasts and booklets. I encourage you and your colleagues to stay up to date on the availability of LLS' Financial Assistance programs, and other resources, using links on these slides.

Slide 104: Free LLS Resources for Your Patients

Through targeted and culturally appropriate programs and services, we are committed to addressing needs of minoritized and underserved communities impacted by a blood cancer and those facing barriers to optimal care. Our materials are available in English and Spanish and our Specialists consult with patients in several languages. If you would like more information for yourself or support for your patients, contact an Information Specialist at 800.955.4572 www.LLS.org/support.

Slide 105: Thank You

Thank you to our presenters & thank you to everyone listening. I hope this information will be helpful as you care for your patients.