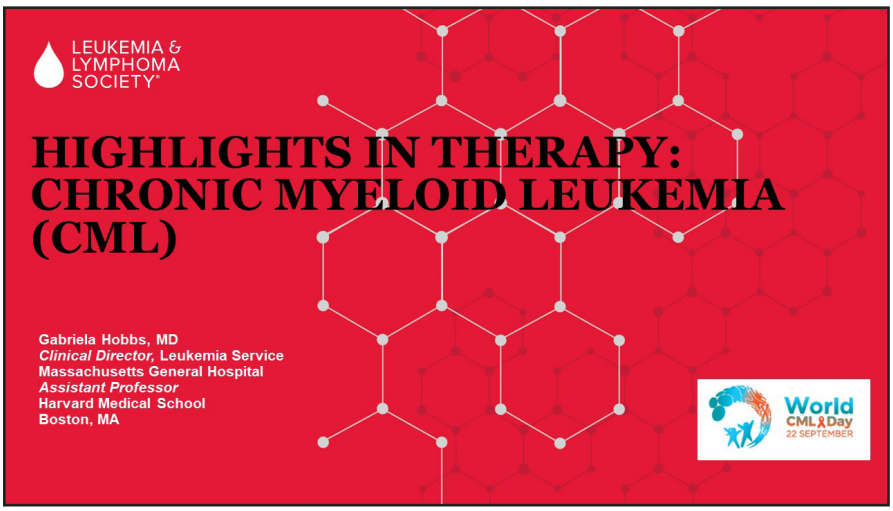


Slide 1: HIGHLIGHTS IN THERAPY: CHRONIC MYELOID LEUKEMIA (CML)

Operator:

Greetings. And welcome to Highlights in Therapy: Chronic Myeloid Leukemia telephone and web education program.

It is now my pleasure to turn the floor over to your moderator, Lizette Figueroa-Rivera. Thank you. Lizette, please begin.

Slide 2: WELCOMING REMARKS

Lizette Figueroa-Rivera:

Hello, everyone. Thank you for joining us today. On behalf of The Leukemia & Lymphoma Society, I'd like to welcome all of you.

As many of you know, LLS helps you navigate cancer treatment and ensures that you or your loved one has access to quality, affordable, and coordinated care.

Outcomes for treatment of CML (chronic myeloid leukemia) have dramatically improved over the past 50 years. While the 10-year survival rates were less than 20% with the use of cytotoxic agents in the 1970s and improved to 50% with bone marrow transplants, the biggest improvements occurred within the last 20 years after the approval of a new class of drugs called tyrosine kinase inhibitors, which we typically call TKIs.

Thanks to treatment breakthroughs pioneered with LLS support, patients with CML can expect a similar lifespan to the general population.

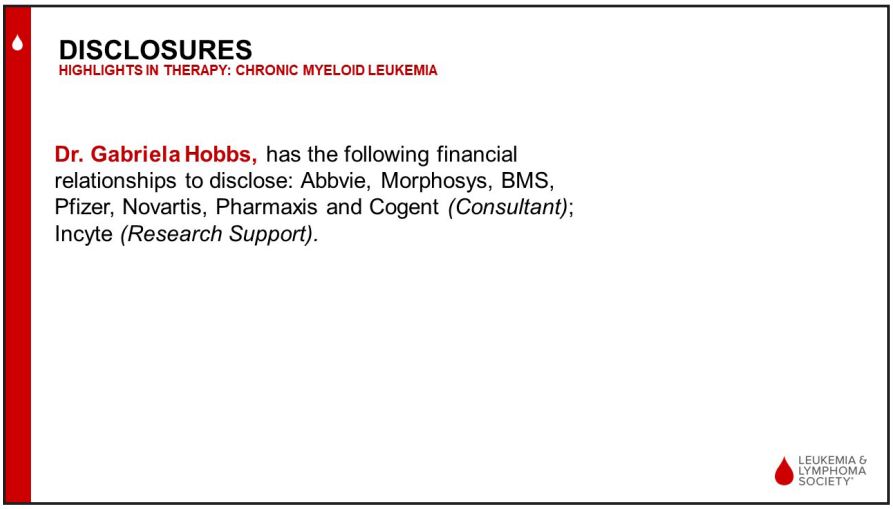
LLS is at the forefront of precision medicine and will continue to accelerate impactful research to improve the quality of life of patients with CML and help make long-term treatment-free remission a reality for more patients.

LLS has invested over $1.5 billion in cancer research since our founding in 1949, leading to nearly every advancement in blood cancer treatment and breakthroughs in immunotherapy, genomics, and personalized medicine.

We will continue to support you, our CML community. Please continue to inform us of what you need and please continue to let us be there for you.

Slide 3: FACULTY

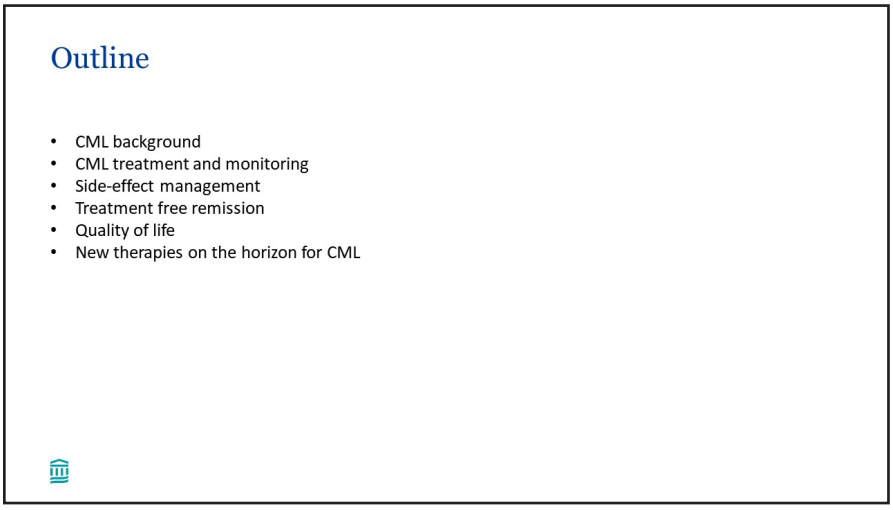
It is now my pleasure to introduce Dr. Gabriela Hobbs, Clinical Director of Leukemia Service at Massachusetts General Hospital and Assistant Professor at Harvard Medical School in Boston, Massachusetts. Dr. Hobbs, I'm privileged to turn the program over to you.



Slide 4: DISCLOSURES

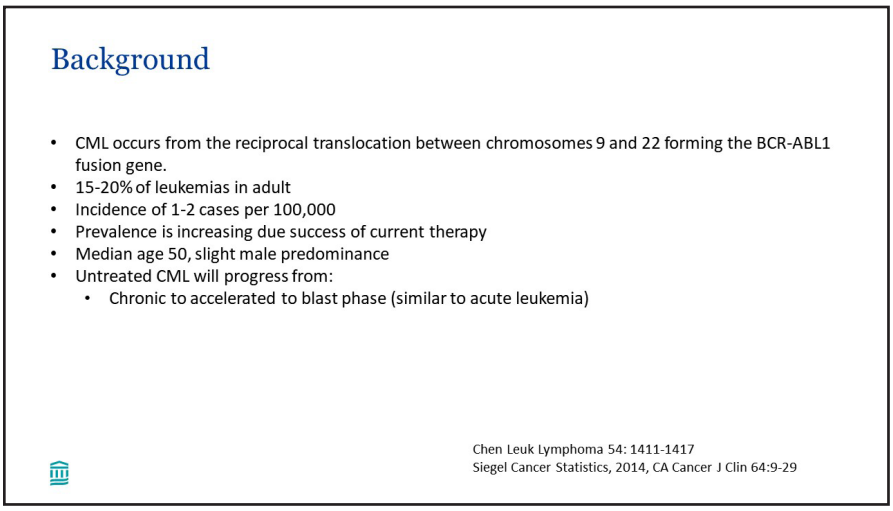
Dr. Gabriela Hobbs:

Thank you so much and thank you for that introduction, and it's wonderful to hear all of the amazing advances that we've had in CML.



Slide 5: OUTLINE

So today I will give a brief overview on chronic myeloid leukemia, just a little bit of background. I'll discuss the approach to treatment, as well as how to monitor patients that are diagnosed with chronic myeloid leukemia. Then I'll spend some time talking about managing side effects, discussing treatment-free remission, also known as discontinuing therapy, and then I'll discuss quality of life, as well as new therapies that are on the horizon for the management of CML. And I look forward to answering questions at the end.



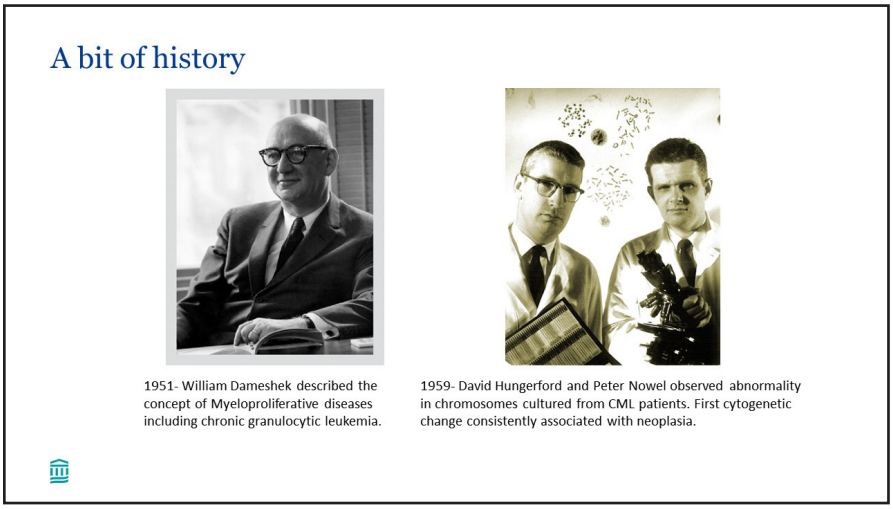
Slide 6: BACKGROUND

CML is a very unique leukemia that is characterized by what is called a reciprocal translocation, meaning one piece of one chromosome goes and attaches itself on another chromosome, forming a new protein called the Philadelphia chromosome or the BCR-ABL fusion gene.

CML accounts for about 15% to 20% of leukemias in the adults, and its prevalence is increasing, as you have just heard, there is some dramatic success in the treatment of this disease.

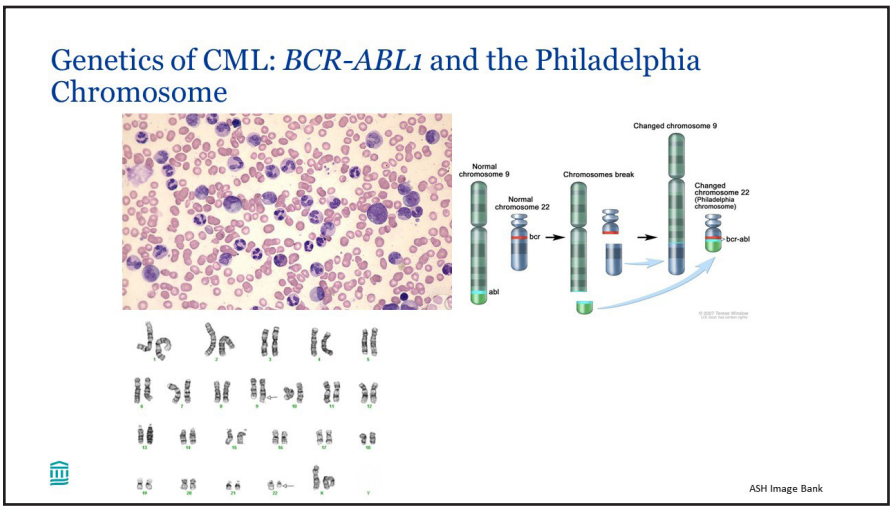
The median age of diagnosis is 50 with a slight male predominance.

Now most patients that are diagnosed with CML will be diagnosed in what's called the chronic phase, but if CML is untreated, invariably it will progress through 3 stages, from chronic phase to a more intermediate stage called accelerated phase, and lastly to a stage called blast phase, although those definitions are currently being revisited.



Slide 7: A BIT OF HISTORY

So now a bit of history. In 1951, a scientist called William Dameshek described a concept of the myeloproliferative diseases in general, which also included what was then termed as chronic granulocytic leukemia, which is now termed as chronic myeloid leukemia. And in 1959, David Hungerford, as well as Peter Nowel, observed an abnormality in the chromosomes cultured from CML patients. And this was the first time that a change in the genetics of a cell of a patient was consistently associated with a disease. So that was pretty novel at the time.



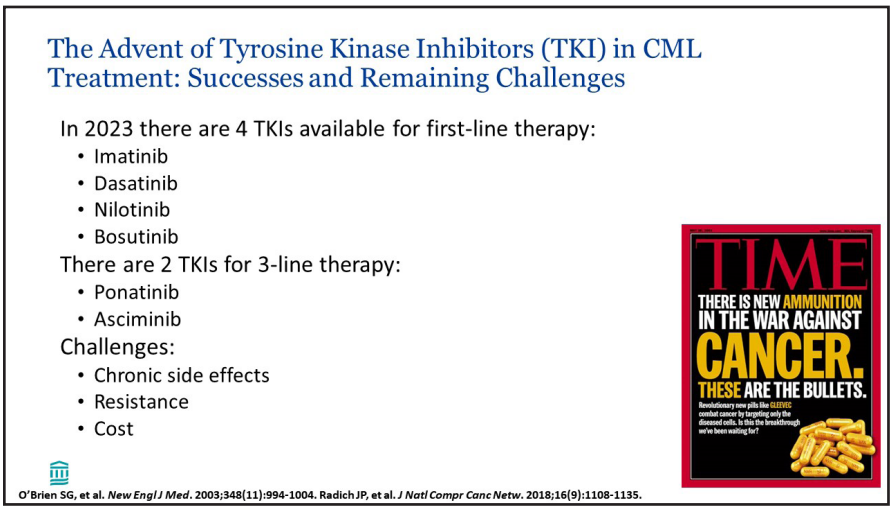
Slide 8: GENETICS OF CML: BCR-ABL1 AND THE PHILADELPHIA CHROMOSOME

So whenever I treat patients with CML, I think it's important to first start talking a little bit about the nomenclature and what are the many terms that we use. And so, first it's good to understand what is this BCR-ABL that we check all the time.

And so, the cells that you can see on the slide are basically what a blood smear looks like from a patient with newly diagnosed CML. And basically what that highlights is that there are lots of those purple cells and those purple cells are white blood cells, but all of them look a little bit different. So basically, there is just lots of different types of white blood cells and that's pretty typical of a new diagnosis of CML.

On the bottom, you see these squiggly things. Those are chromosomes and basically when a patient gets diagnosed we take a picture of all the DNA inside of their cells and what we can tell is that a piece of chromosome 9 attaches to a piece of chromosome 22. Normally chromosomes stay in their place. And so when that happens, it creates what's known as the Philadelphia chromosome or this BCR-ABL gene that creates a new protein and that is something that is very

important for the diagnosis of patients. There is no CML without the BCR-ABL fusion protein. And then we also utilize it to understand how well our patients are doing with therapy or if there needs to be changes done to our therapy.



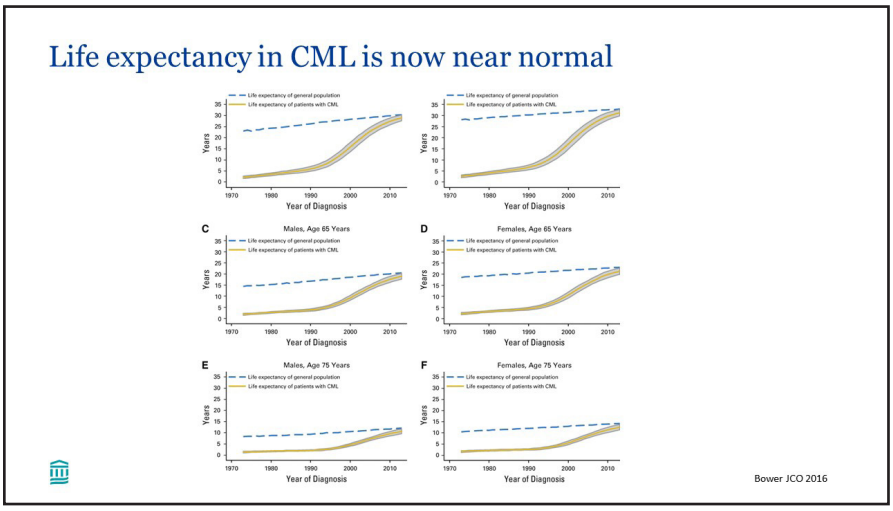
Slide 9: THE ADVENT OF TYROSINE KINASE INHIBITORS (TKI) IN CML TREATMENT: SUCCESSES AND REMAINING CHALLENGES

So, in CML we are really fortunate that we now have a class of medications called tyrosine kinase inhibitors, which have really absolutely changed the face of this disease. The first one to be approved was imatinib (Gleevec®) in 2001, but since then we have a variety of other drugs that are approved.

In 2023 we have 4 TKIs, or tyrosine kinase inhibitors, that are available and approved for first-line therapy in the United States that includes imatinib, dasatinib (Sprycel®), nilotinib (Tasigna®), and bosutinib (Bosulif®).

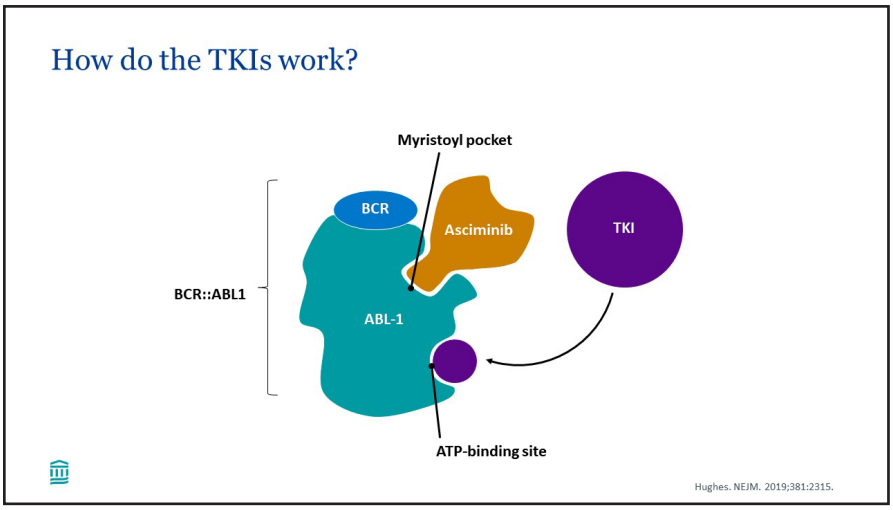
There are also tyrosine kinase inhibitors that are approved for later lines of therapy, ponatinib (Iclusig®) is one of them and asciminib (Scemblix®) was recently approved as well.

Now although we do have a lot of excellent medications, there are still some challenges. Patients must live with chronic side effects associated with therapy, some patients will have resistance to therapy, although thankfully that doesn't happen that frequently, and then cost remains an issue, which we'll discuss.



Slide 10: LIFE EXPECTANCY IN CML IS NOW NEAR NORMAL

Now, outcomes for patients with CML have obviously changed significantly, whereas in the 70s most patients did not survive this disease. And then the 90s, one of the most common reasons for going to a bone marrow transplant was CML, now it is probably one of the least common. And now, life expectancy for patients with CML is essentially near normal, as is demonstrated in these graphs on the bottom of the slide where you can see how over time, over the decades, the yellow line, which is the patients with CML, have basically caught up with their age-match cohorts of patients that do not have CML. And so obviously that is very exciting. I think that with that information we have to treat our patients to ensure that not only do they live well with CML and get to that near-normal life expectancy, but we also balance the side effects of the medicines that they're on with making sure that they live a long time. So we'll talk more about that during our slides.

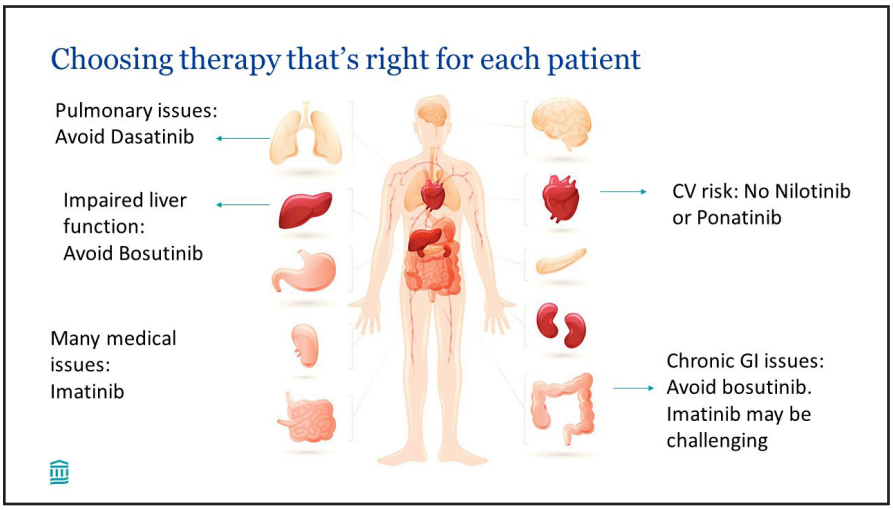


Slide 11: HOW DO THE TKIs WORK?

So we're going to spend some time talking about these medications, but what are TKIs and how do they work?

Here is a little cartoon of that BCR-ABL protein, just a reminder of high school biology, all of the DNA in our body has the ability to give instructions to make proteins. DNA gets turned into proteins, and the BCR-ABL is just like that, so it creates this new protein called BCR-ABL, which is really an enzyme. And it has several different little pockets on it. Basically, BCR-ABL is a protein that is always on, it's an enzyme that is always on, and is basically responsible for leading to uncontrolled growth and the occurrence of leukemia.

Now most TKIs, like you can see in the purple little circle, bind in an area of this or bind meaning attaches or sticks to an area of that protein called the ATP-binding site and basically that helps to shut it off. And then asciminib is novel compared to the others in that it binds in another area of the protein, or it sticks to another area of the protein, called the myristoyl pocket. But basically the result is the same, shutting down the protein and allowing or leading to cell death and to very good control of leukemia.

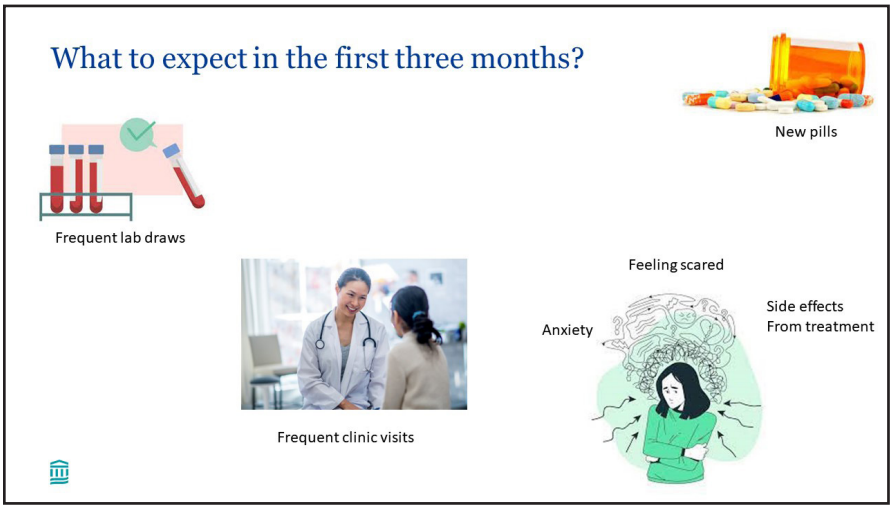


Slide 12: CHOOSING THERAPY THAT'S RIGHT FOR EACH PATIENT

So now that we have several different drugs to utilize and several of them in the first-line, it's important to choose the therapy that is correct for each patient. It's not enough to just put a patient on a tyrosine kinase inhibitor, we have to put a patient on a tyrosine kinase inhibitor that's going to work for them.

For example, patients that have pulmonary issues may not be the best candidates for a medication such as dasatinib. Patients that have a lot of cardiovascular risk factors, that maybe have peripheral vascular disease or diabetes, are maybe not the best candidates for taking nilotinib or ponatinib. Patients that have issues with diarrhea or liver function, then are maybe not the best candidates for bosutinib, for example. And then patients that have a lot of medical issues or may be older, are good candidates for medications such as imatinib.

So it's important for the prescribing doc to know about all of these side effects in order to be able to make a good decision for the patient, to choose the medication that is most likely to work for that patient.



Slide 13: WHAT TO EXPECT IN THE FIRST THREE MONTHS?

So, a patient has been diagnosed and then they speak with their clinician about what medication they're going to be taking, and then what? And so I think it's important to separate treatment into the first couple of months of therapy and then therapy after that.

So, the first couple of months there's a lot going on. There's going to be frequent visits to the clinical team and there's going to be frequent blood draws, because as a person is getting first started on these medications, don't be

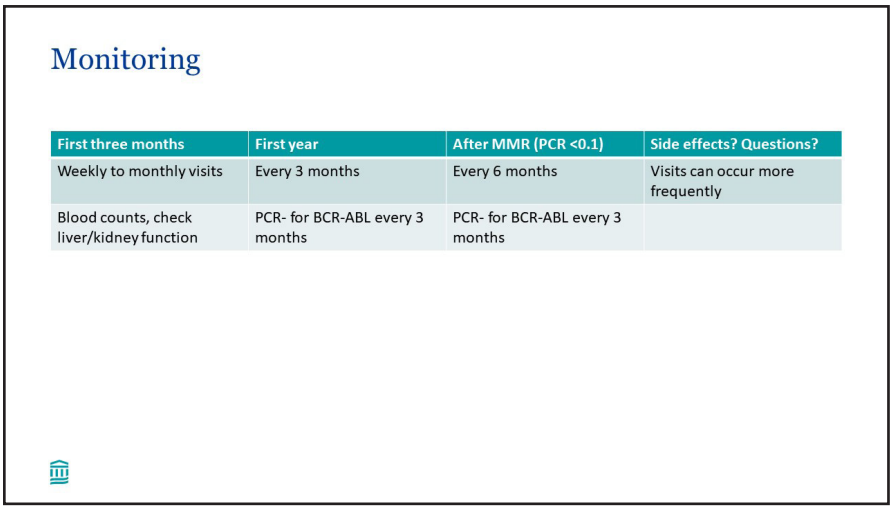
surprised if there's more side effects and also the blood counts can change significantly in those first 3 months. And so, it's important to be monitored closely by having your blood levels checked frequently.

Of course, in those 3 months there's a lot of emotional things that are going on at the same time. No matter what a doctor or clinician may tell you about outcomes and prognosis, it's still a new diagnosis and there's still new medications to get used to. Sometimes, especially at the beginning of treatment, there may be supportive medications that may need to be taken in order to allow you to better tolerate the new medication, the TKI that was given specifically for the leukemia. So all of a sudden, whereas you maybe didn't take that many medicines before, now you have new medicines to take every single day.

It's also not uncommon, especially in these first 3 months, to feel anxious, maybe feel scared, and also to be experiencing new side effects from medications.

Slide 14: THE GOOD NEWS IS...

The good news is... it gets better. And hopefully, this talk will help you understand kind of what to expect, to help you to know what to expect moving forward, and to feel better if you were recently diagnosed.



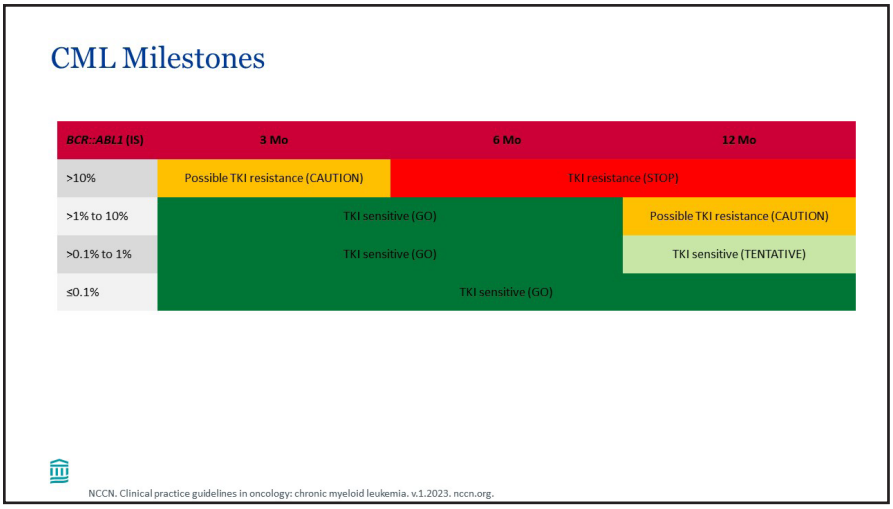
Slide 15: MONITORING

So like I mentioned, the first 3 months of therapy usually require frequent monitoring. And it's not exactly the same for everybody, so if you're not exactly being monitored this way it doesn't mean that it's the wrong thing. But in the first

3 months, it's not uncommon to have weekly or monthly visits and then to have blood counts checked, which include the levels of the white blood cells, red blood cells, and platelets, but also checking liver and kidney function, as some of these medications can sometimes impact that.

But then after you make it through the first 3 months, assuming everything is going well, you're tolerating treatment well, side effects are well managed, etc., then patients really only need to be seen every 3 months. And at these 3 month intervals, in addition to checking the blood counts and to also periodically checking the kidney and liver function tests, the key test really is that BCR-ABL test that we were talking about before, to monitor how the disease is responding to treatment.

Now once a patient is in what's called a major molecular remission, or an MMR, meaning that the level of that BCR-ABL test is less than 0.1%, patients can be seen every 6 months. And this only, of course, has to be the case if a patient is doing very well, if there aren't questions, side effects, or other issues that need to be addressed. And if there are any other issues, then certainly those visits can happen more frequently. But this is just kind of a general what to expect in terms of visits, which I think is helpful to orient patients and to let you know that although there may be periods during the diagnosis that visits are more frequent, that doesn't always have to be the case.



Slide 16: CML MILESTONES

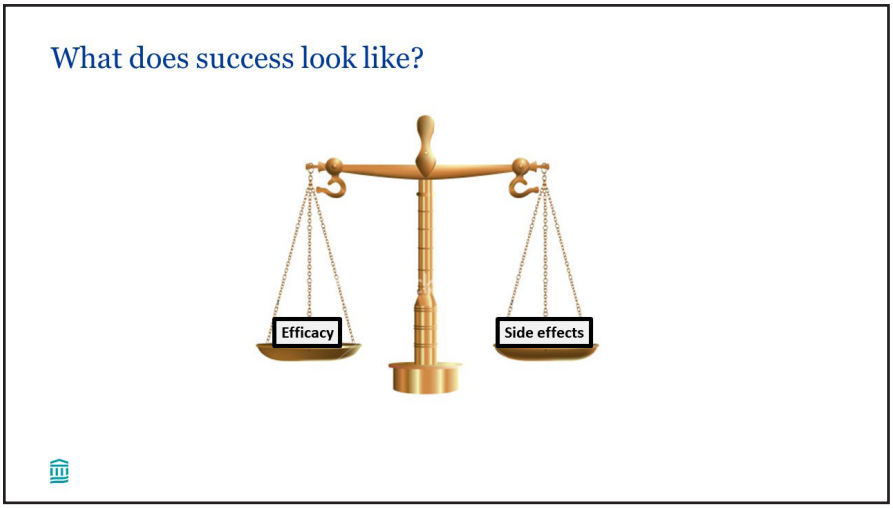
Now this slide is adapted from the NCCN (National Comprehensive Cancer Network), which is the guidelines that are utilized by many providers in the United States and across the world, to help manage patients with CML. And I'm putting this here not to overwhelm anybody, but basically to give them a sense of what are we looking for in terms of success to treatment and how are we defining success.

And so as I mentioned at the beginning of this conversation, the BCR-ABL test, which is something that can be done from the blood, it doesn't require a bone marrow biopsy, is something that we monitor pretty frequently. And basically we have this color-coded algorithm to give us a sense of: is this patient doing okay? is this patient somebody that we need to monitor more closely? or is this a patient where we need to be worried? If the PCR (polymerase chain reaction) levels are in the green, then we're good to go. But if that patient falls within the yellow boxes, then it's a person that we may need to monitor more closely, and if it's in the red, then we really have to stop what we're doing and reconsider another treatment.

So basically to summarize this algorithm, what we want to see is that that PCR test that is usually pretty high at diagnosis, sometimes so high that a number can't be reported, just says greater than assay, we want to see that test go to below 10% in the first 3 months. There are some situations where we may wait a few more months if that test didn't go all the way below 10%, but generally we want to see it less than 10%.

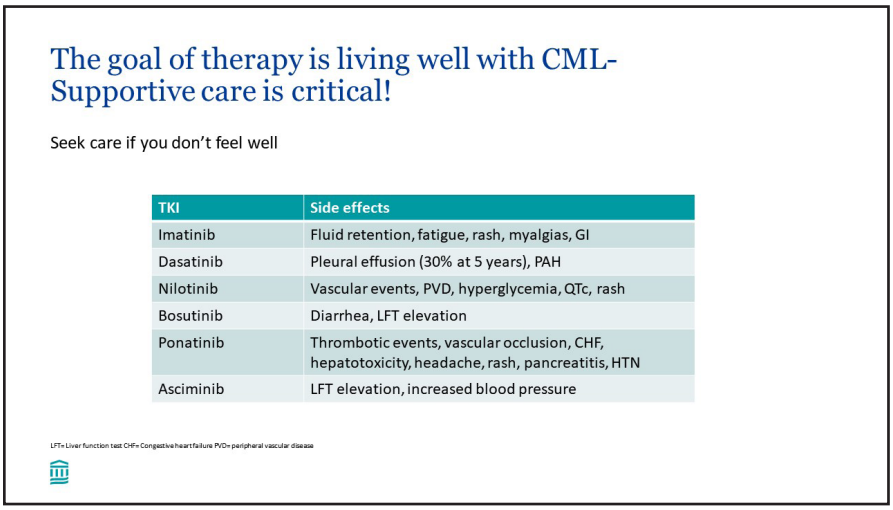
In the first 6 months we want to see it around 1%. And then after the first year, we want that level to be less than 1%.

Now if we're considering discontinuation of treatment, which I'll talk about in a second, we want that level to be much lower. We want it to be at least 0.01. And we need it to be at that level for at least 2 years in order to consider discontinuation. But in order to consider discontinuation, a patient needs to be treated for a total of 3 years but the last 2 need to be at that level of 0.01 or lower.



Slide 17: WHAT DOES SUCCESS LOOK LIKE?

So, success doesn't just mean that the numbers look good. Very early on in treatment the CBC or complete blood count will normalize, and it's likely too that at 3 months, in 6 months, and 1 year will meet those landmarks, but efficacy also needs to be balanced with side effects. And so that part I really want to emphasize. We can't have the treatment or the cure of the disease be worse than the disease itself. So I think balancing efficacy and side effects is really so important.



Slide 18: THE GOAL OF THERAPY IS LIVING WELL WITH CML – SUPPORTIVE CARE IS CRITICAL!

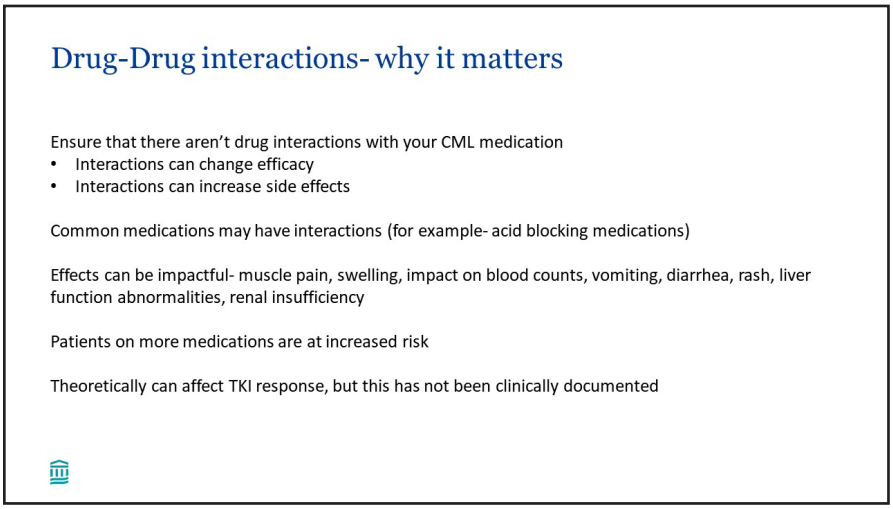
So like I said, the goal of therapy is living well with CML. We don't just want people to live, we want them to live well, to feel like they're living a normal life basically. And so for this, really supportive care is really important. If you or a loved one that you care for with CML is not feeling well, it is important to seek care. It's important to have a sense of what are some of the common side effects that I can expect from my medication. Like I mentioned before, some of these side effects tend to occur at the beginning and then go away, but there are certain side effects that can pop up while you're on treatment, and so knowing about this a little bit is important to know when to seek care. But in general

I would say if something's going on, something seems unusual or different, or you're not feeling well, it's definitely never the wrong thing to contact your healthcare team.

So here I've listed just a few of the common side effects of many of these medications in order to know exactly what to look for. I don't have to go through all of them, but some that are of note, just for example, many of these medications can cause fluid retention or make people feel a little puffy. Good to know that that's something that's associated with them. Usually this occurs at the beginning of treatment, and so if it occurs later on in treatment, maybe something else is going on and that's important to reach out to the clinical team taking care of you.

And if you're feeling short of breath, for example, and you're on dasatinib, it's important to keep in mind that up to a third of patients may develop fluid around the lungs and that may require that treatment is interrupted until that gets better.

And so having an awareness of what the potential side effects are is important, just so that you know what to look for, but in general, like I said before, if you're not feeling well it's never the wrong thing to seek care.



Slide 19: DRUG-DRUG INTERACTIONS - WHY IT MATTERS

So another important aspect of caring for folks with CML and of living with CML is to be mindful of the fact that these medications may interact with other drugs. And so, why does this matter? We need to make sure that we aren't taking medications that interact with our CML medicine because these interactions could potentially affect the efficacy of the CML medication, and it can also and more common and more likely actually, they can increase side effects. And so of course, if we have a medicine that already has side effects, we don't want to make that worse.

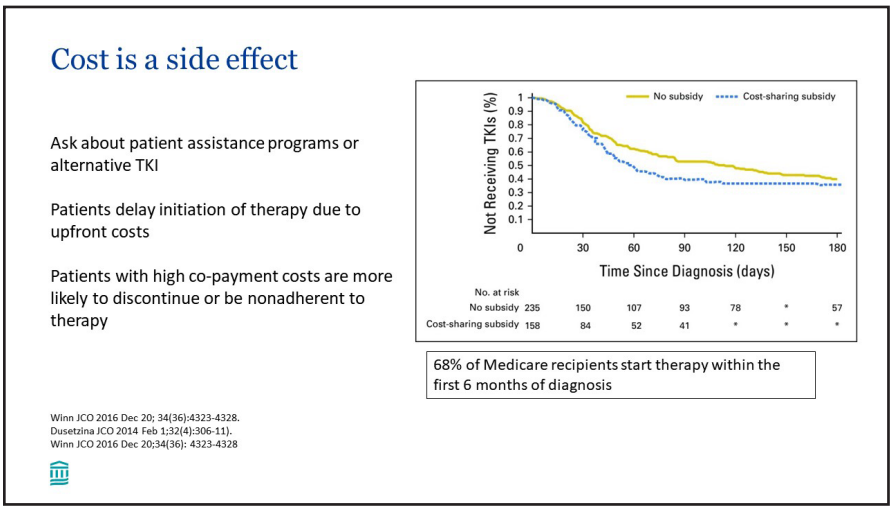
And it's important to note that there're some common medications, like for example acid-reducing medications like proton pump inhibitors, that can really interact with these medications. And so, it doesn't mean that you can't take these medications, it just means that it's an important conversation to have with your clinician. Sometimes it is possible to take them, we just have to take them differently.

So any medicine that you're on, it's important to bring it up to either the primary care doctor that may be prescribing it or your oncologist in general when you're having a visit with them.

These effects can be impactful, like I mentioned, because it can worsen side effects of the medications that you're already on and then can make some side effects worse, like muscle pain or swelling, it can change blood counts, etc. So be very aware of the medicines that you're taking, and this can even include supplements or other things that aren't prescribed. And so, just be cautious of medications that you may be taking.

And obviously patients that are on many medications, which unfortunately is very common in the United States, are obviously at increased risk.

In theory, like I mentioned, these drug-drug interactions can affect response, although that really hasn't been clinically documented, but it's best not to test that, I think.



Slide 20: COST IS A SIDE EFFECT

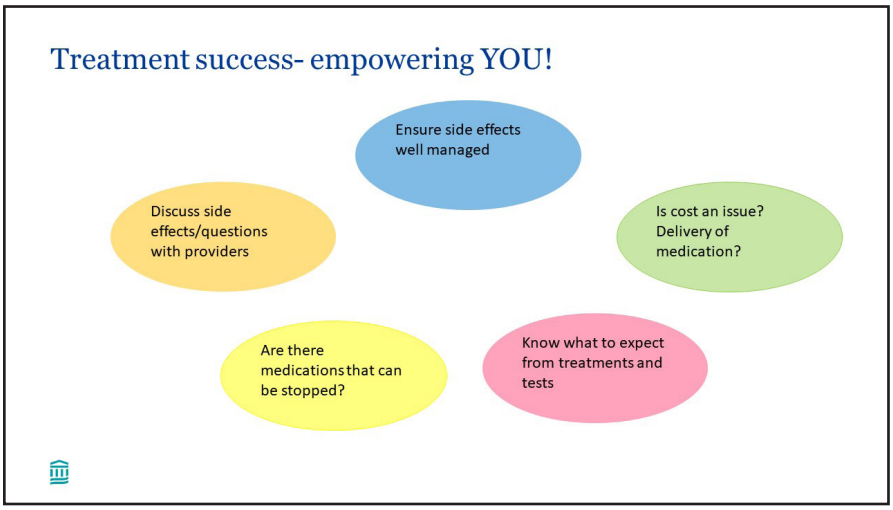
So, another important side effect of these medications is cost. And so although these medications have been around for a long time, at least in the United States, cost remains a considerable issue for some patients.

It's important for patients to know that they have options. It's possible, and I've experienced this with a lot of my patients, that one insurance plan may not cover one medication, but they may cover another, so each insurance plan is different in what medications they approve in first-line and which ones they do not, and so know that you have options. There's also, many of these medications have what are called patient assistance programs or vouchers that make that medication free of charge in the first month.

And cost really is a very important component because of course if we're not taking the medicine then obviously we can't have good outcomes.

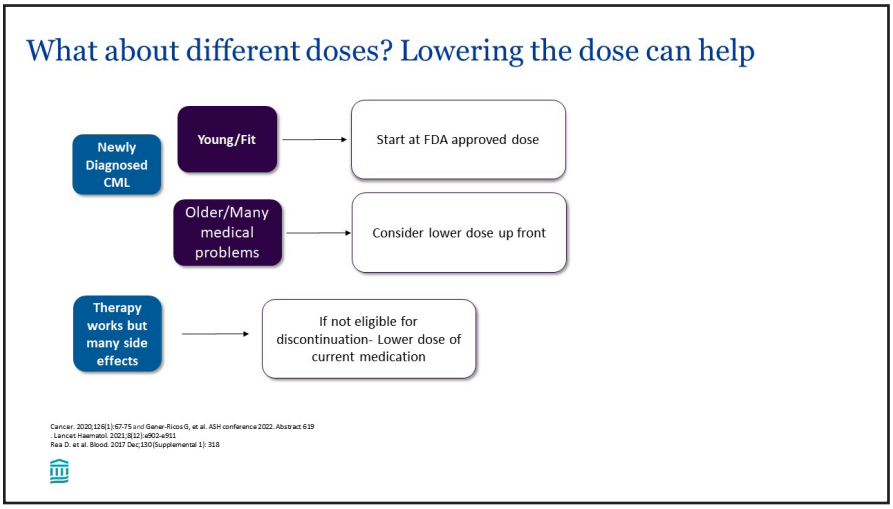
Many patients in the United States may delay initiation of therapy due to these up-front costs. And there have been studies where if the cost of the medicine is subsidized, patients are more likely to start their medication on time than if the cost is not. And that makes sense. And so, patients that have high copayments are more likely to discontinue their medication or to not take their medication as prescribed.

So, one of the things that I like to talk about with my patients and in forums like this, is to go to the clinic visit prepared with questions so that you don't forget to ask certain questions and also so that you don't lose your nerve at the end of the visit and don't ask questions that maybe you think are embarrassing. And so cost is one of those things that I want you to go into that clinic visit prepared to ask and to make sure that if there is a resource available to you to help you with those medications, that you do get that question asked. That is definitely an important thing and it's fair game to talk about that during the clinic visit.



Slide 21: TREATMENT SUCCESS – EMPOWERING YOU!

So as I was mentioning, treatment success means that you as a patient or a caregiver needs to be empowered. It's important to make sure that side effects are well managed. If cost is an issue or if you have issues getting that medication every month, it's important to bring that up during your visits or to call in between visits as well. It's important to know what to expect from the treatment, know what to expect in terms of tests, how often you'll be going to the doctor, how the first couple of months differ from the later months. It's important to know what medications you're taking and should some of those medications be stopped. And, it's important to just generally be aware of the fact that these medications can interact with other medications. So the more knowledge you have and by joining this webinar hopefully you'll have more information to be empowered, because I think that that's a really important part of treatment success.



Slide 22: WHAT ABOUT DIFFERENT DOSES? LOWERING THE DOSE CAN HELP

Now a common question that I get is, do I have to be on the full dose of this medication? And so, this is an area where I think guidelines are probably going to evolve over the next couple of years and there's been some studies that demonstrated that some of these medications don't actually have to be given at the full dose. We generally prescribe them at the FDA (United States Food and Drug Administration) approved dose because that's how they were studied, and so that's where we have the most data. But now that we have many years, and in some cases decades of experience with these medications and with managing patients with CML, we know that we don't need a full dose in order to have success in terms of treatment. And like I mentioned before, having a lower dose of treatment can sometimes really help in order to make treatment easier.

So here's my proposed approach or the way that I approach management of my patients.

If I have a newly diagnosed patient and this person is young, doesn't have other medical issues, they're fit, I'll generally start them on the FDA-approved dose. I've changed that a little bit for some medications, in particular dasatinib, because there's some data now, some studies that have shown that it's safe and equally effective to start at a lower dose, but generally speaking, younger fit patients can start at an FDA-approved dose.

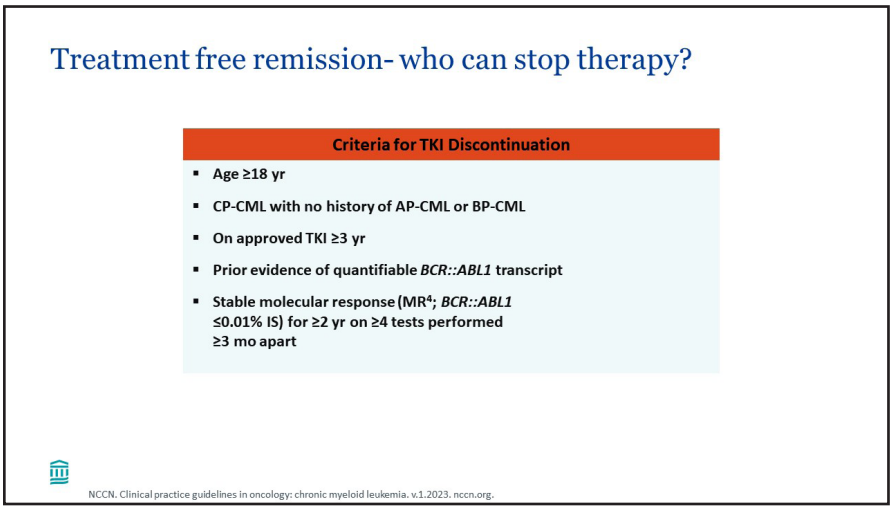
Now patients that are older, patients that have many medical comorbidities, in my experience have a much harder time tolerating full dose of a drug. There's nothing wrong with talking about this with your provider when you're getting started on a medication, especially those that are over the age of 70, full dose of a drug can be really, really difficult to tolerate, and so my preferred approach would be to consider a lower dose up front and then to increase the dose if needed. It may not necessarily need to be increased if we're meeting those landmarks that I was talking about in terms of the BCR-ABL levels being where they need to be at the different time points.

Now, there're sometimes where patients are on a full dose of a treatment and they've met all their landmarks, the BCR-ABL level is falling nicely, but the person has a lot of side effects and those side effects maybe don't get better by giving other supportive medicines like nausea medicines or diarrhea medicines or that kind of thing. Those patients in my mind are excellent patients, or excellent candidates, for dose lowering. So if you're on the full dose of a medication, you have lots of side effects, but that PCR level is very low, I think it's pretty safe to lower the dose of that medication to see if that improves the side effects, because it usually does.

Of course for some patients we can talk about discontinuation, but if we're not yet at the point where discontinuation is a good option, then lowering the dose is really, really helpful to ensure that patients are living well with their CML.

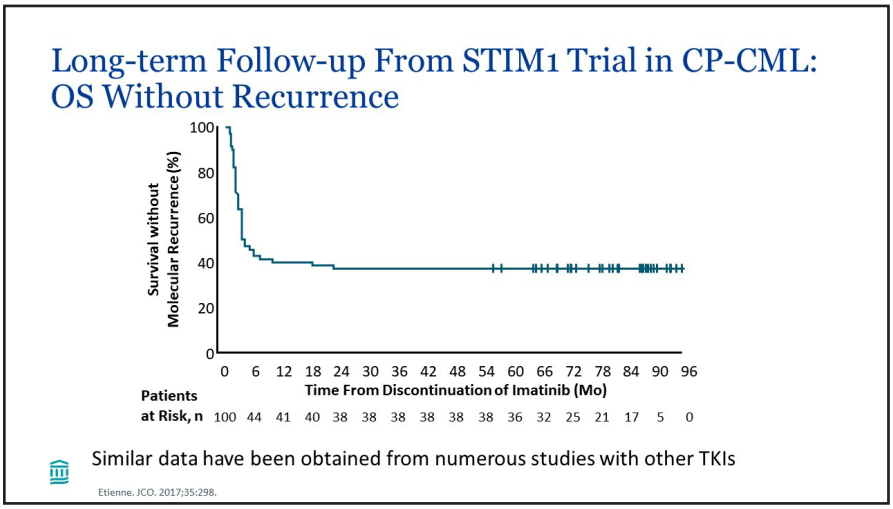
Slide 23: TREATMENT FREE REMISSION

So there's a relatively newer concept called TFR or treatment-free remission, which is also known as stopping your therapy, and many times I get a look from my patients that says wait, what are you talking about? You've been telling me every visit that I come that I need to take my medication, that I can't miss a single dose, and now you're talking about stopping therapy?



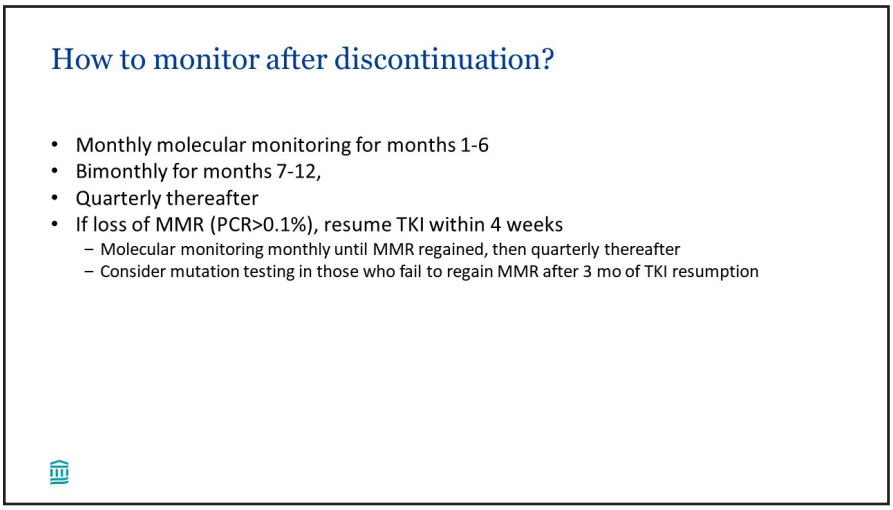
Slide 24: TREATMENT FREE REMISSION – WHO CAN STOP THERAPY?

So, who can stop therapy and why would anybody recommend that? Well, there've been many, many, many studies that have shown that stopping therapy in the right patient is actually safe. So patients that are over the age of 18 who have chronic phase CML, who have been on an approved therapy for at least 3 years and the longer the better, to be honest, that have stable responses to treatment and especially those last 2 years are in a deep remission, meaning a level of 0.01 or deeper, the deeper the better, are candidates for discontinuing their treatment.



Slide 25: LONG-TERM FOLLOW-UP FROM STIM1 TRIAL IN CP-CML: OS WITHOUT RECURRENCE

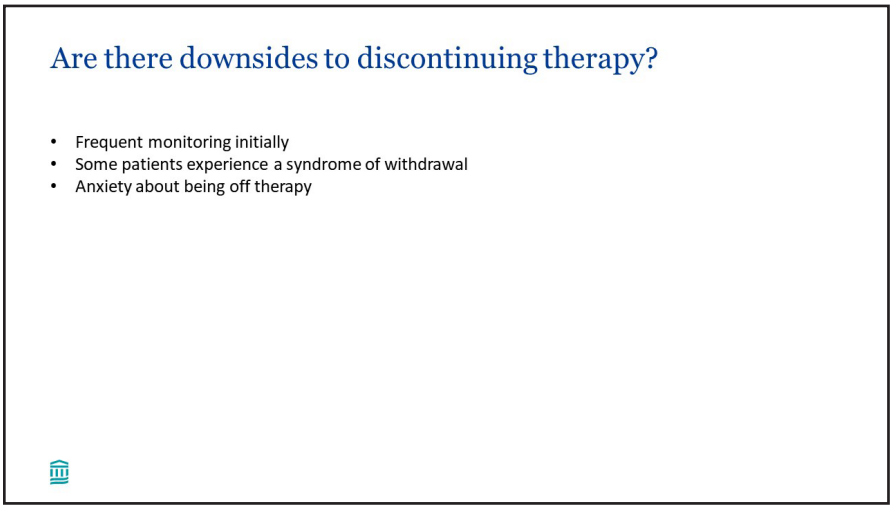
So, here I'm showing the results of the STIM study, which was the first study that tested out this hypothesis of whether or not it was safe to stop therapy. And what we learned from the STIM study, and what we've learned from other studies, is that when patients relapse they tend to relapse very quickly in the first 6 months of therapy, and then the other half of patients that don't relapse in the first 6 months of therapy generally are able to stay off of their medication for many, many years, but there are some patients that will have a return of that BCR-ABL later on in treatment. And so, it's important when a patient stops therapy that monitoring does continue, so that when the level becomes detectable again, patients get started on medication again.



Slide 26: HOW TO MONITOR AFTER DISCONTINUATION?

So a really important part about discontinuing therapy is that patients really do need to be monitored very closely. In the first 6 months of therapy patients need to have that BCR-ABL test done every single month. After that, it's every 2 months from month 7 through 12. And after the first year, it's every 3 months. And that really should continue indefinitely because there are some patients that have been off of therapy for many years that can then have a recurrence of the BCR-ABL that maybe wasn't detected before and then becomes detectable after some years.

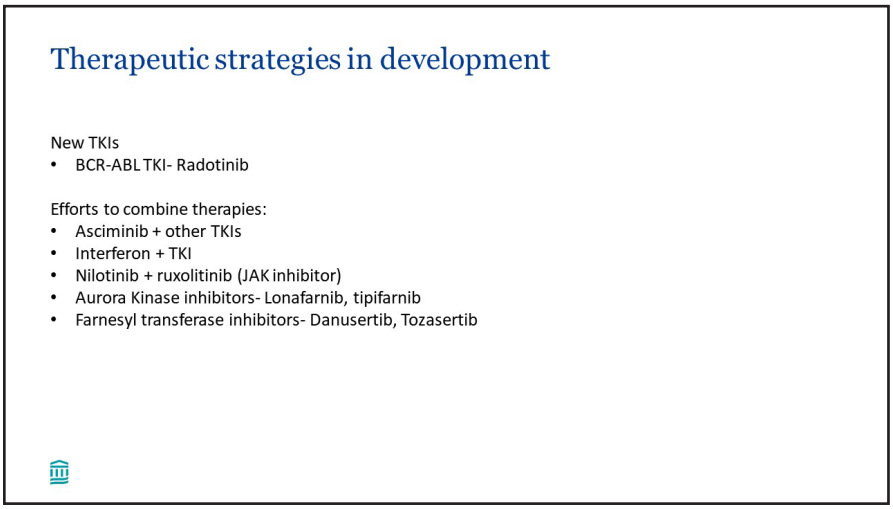
Now, when a patient has a PCR level that then goes above 0.1, they should restart treatment within the next 4 weeks. Now what treatment should a patient discontinue? If the patient was doing just fine with the medication that they were on before, they can go ahead and restart the same medication. But if they weren't doing well with that medication because of side effects, then this presents a good opportunity to change medicine, but patients don't have to change medicine otherwise because the same medicine that was working before will work again.



Slide 27: ARE THERE DOWNSIDES TO DISCONTINUING THERAPY?

So, are there downsides to stopping therapy? Well, initially you do require frequent monitoring, so that can be difficult for some patients with busy schedules. Some patients experience what's called a withdrawal syndrome, some patients can have kind of like joint pains or muscle aches. This tends to be short-lived. Sometimes it requires that patients take medications like ibuprofen or other NSAIDs (nonsteroidal anti-inflammatory drugs), rarely they should take prednisone if the symptoms are really significant, and then in very rare instances it's a syndrome that doesn't go away for many months.

And another symptom that really isn't discussed that frequently is anxiety about being off therapy. I've had some patients that just don't like the idea of not being on a medication that they know is so important for them. So some patients, it's not for them and that's okay.



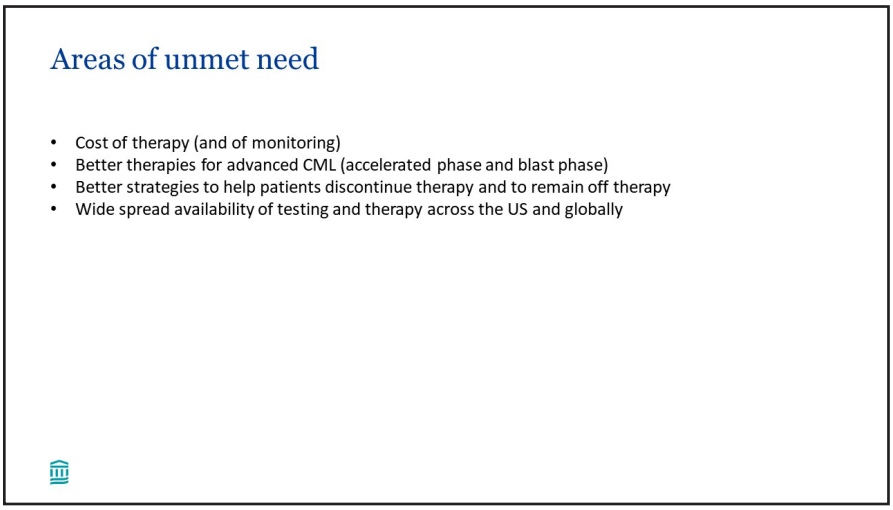
Slide 28: THERAPEUTIC STRATEGIES IN DEVELOPMENT

So, in addition to all the wonderful medications that we have now, there are also new medications that are in development. There's a new tyrosine kinase inhibitor called radotinib that's being studied, and then there's also efforts to combine therapies. Asciminib, the newer tyrosine kinase inhibitor that was just approved is being studied in combination with other drugs, and the reason why this makes sense is, remember that little cartoon I showed you, asciminib blocks the BCR-ABL in one part of the protein and the other medications block it in another part of the protein, so investigators have wondered if we can block those 2 sites together, if maybe we have better results.

A medication called interferon was previously used to treat patients with CML and so they're combining it with TKIs.

Other medications, like immunomodulatory medicines or checkpoint inhibitors, are being tested as well.

Medications like ruxolitinib (Jakafi®), which is what's called a JAK inhibitor, used for medication for diseases that are similar to CML, called myeloproliferative neoplasms, are being used in combination with CML medications, among other medications as well. So there's definitely still interest in doing research in this disease, to help patients to get into deeper remissions, faster remissions, and to be able to hopefully come off of therapy more frequently and stay off of therapy.

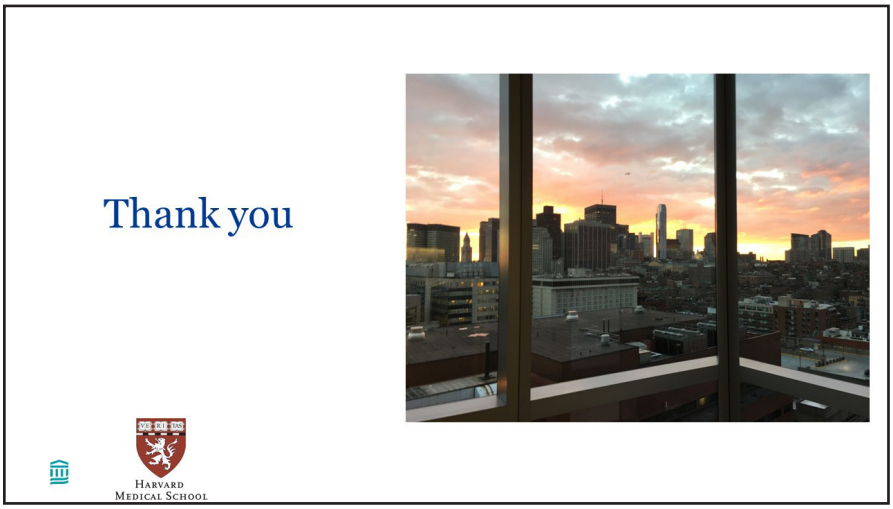


Slide 29: AREAS OF UNMET NEED

So, are there still areas of unmet need in this disease? I think that the cost of therapy is still an issue. And then monitoring is sometimes challenging, especially for patients that don't live near specialized medical centers. We definitely still need therapies for more advanced CML, which I did not talk about today.

And then an area that I would really like to see improved is better strategies to help patients to stop their therapy, and not only that, but to stay off of therapy. We have many patients that meet all the criteria to stop therapy and then a few months later the disease comes back. And so, it would be great if we had some strategies to help patients to stay off of therapy for longer periods of time.

And of course, although in the United States we're very fortunate to have many medications, in the world at large this isn't really the case and many areas still don't have availability of many of the TKIs, and testing is really very problematic in low resource areas.



Slide 30: THANK YOU

Thank you so much for your attention and I really look forward to answering some questions now.

Slide 31: ASK A QUESTION

Ms. Figueroa-Rivera:

Thank you so much Doctor for the great information that you provided today about CML.

We'll take the first question from our web audience. Doctor, Jenella asks, my daughter was diagnosed at 12, she's now 19 years old, would she be able to have kids? She's been on TKIs since diagnosis, both imatinib and bosutinib, and has only ever had a partial cytogenetic response. She does know that all depends, every different case is different but can women potentially go off TKIs and safely get back on?

Dr. Hobbs:

Great question. And so now that we have information about treatment-free remission that's actually really helped me to treat my patients that are considering pregnancy, because we know that if we meet certain landmarks, then stopping therapy can be safely done. Now the challenge with pregnancy, of course, is that if that PCR level becomes detectable, well, we can't just go ahead and restart the medication during pregnancy. But it does give us a little bit of a guide. And I think the most important thing to note is that TKI discontinuation can be done with some monitoring. The longer a patient has been on a treatment and the longer that that person has been in a deep remission, the higher the likelihood of being able to stay off of their medication during pregnancy.

It's also important to note that these medications by themselves do not really necessarily affect fertility. Of course, that's not an area that's been studied. There's really no reason to think that they affect fertility specifically.

So as a general answer, yes, patients with CML can definitely get pregnant and they just will need to stop their medication during pregnancy.

Now of course, the key thing that you noted there, and that's something that I think really should be discussed with the treating doctor, is why has the response not been deeper. Now that your daughter is 19, there are other drugs that can be considered, and I would encourage you to talk about that with the doctor to make sure that her remission is as deep as it should be.

Ms. Figueroa-Rivera:

Thank you so much. And we'll take the next question from our telephone audience, please.

Operator:

Next question from Candace, go ahead.

Candace:

What do you advocate when you take your patients off medication? Do you advocate a bone biopsy prior to their discontinuing medication? The reason I'm asking that is because my oncologist requires a bone biopsy before she will take her patients off of medication.

Dr. Hobbs:

I'm glad you asked that question. So if you look at the guidelines and you can go to the NCCN guidelines online, there is no mention whatsoever about needing to repeat a bone marrow biopsy, not only in the setting of stopping therapy, but in general. If a patient has a PCR of less than 1%, there's really very little utility to doing a bone marrow biopsy, so absolutely not, a bone marrow biopsy is not required in this instance at all.

Ms. Figueroa-Rivera:

Thank you. And Kelly is asking, I have chronic fatigue, brain fog, and dizziness daily after stopping imatinib, which I stopped 2 months ago at my doctor's direction due to these side effects. I will likely go on a different TKI if my next PCR shows detectable. Is it common to have fatigue and my other symptoms that long after stopping my TKI?

Dr. Hobbs:

So that's an interesting question and if the reason for stopping imatinib was because of those symptoms and those symptoms persisted after you stopped, then I think it's really important to consider that it may not be the medication that's causing it. Generally speaking, when we see withdrawal syndrome, that's associated more with joint aches and bony pain, not so much the fatigue and brain fog, and so I do think that it's important to make sure that nothing else is being overlooked, as I wouldn't expect those symptoms if they were related to the medication, I would expect you to feel better almost right away.

Ms. Figueroa-Rivera:

Thank you. And we'll take the next question from the telephone audience, please.

Operator:

Thank you. The next question comes from Deanna. Go ahead, Deanna.

Deanna:

Hi, thanks for taking my call and thank you for your presentation. I'm wondering how does one discern a change of med when one hasn't had the numbers – you're still in a safe range, the side effects are manageable, not fun, but manageable, and how does one discern when to change the med?

Dr. Hobbs:

Great question. I think it sort of depends on where in your treatment you are. So initially in treatment those first couple of months, I think it's to be expected to have side effects. And during those first 3 months, I think working with your care team to make sure that if nausea is a problem, that you have those medications, or diarrhea is a problem, you have those medications, but if it's more than past the first 3 months, then we have a little bit more to play with, especially if patients are meeting their landmarks. So if at 3 months the PCR is 1% or something like that, then that's a patient that's responding well to treatment and perhaps I would consider lowering the dose of the medication. And so really my approach, generally speaking, is to do everything possible to help that patient to tolerate that first medication that they're on, including all the supportive care, and then considering lowering the dose of the treatment before I switch a patient to another medication.

So, although we are obviously very fortunate in CML that we have lots of great therapies, the amount of therapies that we have are not indefinite, and so we really want to make sure that our patients live a normal life expectancy, and I don't like to just cycle patients through many different medications. A very common consult I get is patients that have been on every single medication and really all it requires is sometimes a tweak of the supportive care or just lowering the dose a little bit, and that can help control those side effects. So that's generally my approach. Good supportive care, considering lowering the dose, and if those things don't work, then we say, alright, forget it, we're at the lowest dose of this medication, still miserable, let's switch over to another medication.

Ms. Figueroa-Rivera:

Thank you. And Nancy is asking, before trying treatment-free remission, is it better to reduce dosage first or stop TKIs cold turkey?

Dr. Hobbs:

What a wonderful question, Nancy, thank you for asking that. So it really depends on what's going on. I think that, although I really do like to talk to patients about treatment-free remission, I feel like it's a carrot that's difficult to dangle in front of patients honestly. So, 3 years is a long time to wait until a person can stop their therapy. And so, I would rather a person feel well and have adequate management of their disease with a low dose of a medication for many years, than be miserable for 3 years and then try to discontinue therapy.

If a person is really just not feeling well with their medication, I would try to lower the dose of the drug. And we know that doesn't really matter what dose of the drug you're taking, if at 3 years that PCR level has been consistently less than 0.01, a person can still stop therapy. And actually when patients are on medications that are better tolerated, patients are more likely to take that medication continuously, and so potentially the efficacy is the same.

Ms. Figueroa-Rivera:

Thank you. And we'll take the next question from our phone audience, please.

Operator:

Thank you. The next question comes from Betsy. Go ahead, Betsy.

Betsy:

Yes. I am 84, I'm in remission, but I have had lung cancer and consequently I take prednisone quite often or am put on prednisone. Doesn't that have an adverse effect to my blood test?

Dr. Hobbs:

Great question Betsy. The prednisone itself shouldn't impact your CML blood test. It may make the white blood cell count look a little different, but the CML test itself should not be impacted at all by the prednisone that you're taking.

Ms. Figueroa-Rivera:

Thank you, Betsy, for the question. Our next question, Steve is asking, how long should a patient stop one TKI before starting another TKI?

Dr. Hobbs:

If a person is switching from one medicine to another, it really depends on what's going on. If a person needs to recover from a specific side effect or something like that, if they have a lot of GI discomfort, for example, I would say, probably stop the medicine and give it a few days until the symptoms are better before starting something new, just to make sure that we actually give the new medicine a fair chance. Otherwise there's really no reason to give a lot of time in between treatments and you can just stop a treatment and start the next one the next day.

Ms. Figueroa-Rivera:

Thank you. And Edwin is asking, how common is it to have another cancer later in life if you have CML?

Dr. Hobbs:

That's a good question and doesn't really have a clear answer. There's been some kind of large studies that have maybe hinted at the fact that CML patients are maybe at higher risk for having other cancers, but the truth is that those studies are kind of inconclusive and it's hard to know if that's just because CML patients are living longer. And so, what I would say is there's nothing different that needs to be done if you have CML in terms of monitoring for other cancers, but it is good to make sure that you're up to date with healthcare management, so having mammograms, having colonoscopies, Pap smears, those kinds of things are definitely very important.

And, I always try to find a way to include this in some answer, and so obviously lifestyle modification is also so important. Some of these medicines may have adverse cardiovascular events, and so living a healthy, active lifestyle is also helpful, not just to manage those cardiovascular side effects, but also to prevent many cancers that we know are associated with excess weight.

Ms. Figueroa-Rivera:

Thank you. And we'll take the next question from our telephone audience, please.

Operator:

Thank you. The next question comes from Barbara. Barbara, go ahead.

Barbara:

Oh, hi, I'm just recovering from pancreatic and spleen surgery. I had to have half of it removed and they believe it was from the Tasigna®. And I was just having side effects, such as bone pain, muscle pain, and joint pain. And I'm just wondering if there are any statistics of how many people who have come off the TKIs, because I cannot go on it again, but my numbers are very good, I'm still in remission and it's been a few months. If there are others, or other information and data about how many or how long this pain might last from the side effects from coming off the Tasigna?

Dr. Hobbs:

I think I need some clarification on that question. So nilotinib or Tasigna can cause pancreatitis and I'm trying to understand if that's what caused the issues with your pancreas that required surgery? And so that recovery is now independent or not related to the Tasigna. I mean the pancreatitis was related of course and that just takes some time to recover. But in terms of the joint aches, muscle aches, and that kind of thing, if that's something that you did not have with the Tasigna and you now have after stopping the Tasigna, then that's a withdrawal syndrome. And like I mentioned before, usually those side effects only last a few weeks. Sometimes patients have it last a little bit longer and that can be months. And so it's important to figure out how to manage that. Initially the first treatment would be something like ibuprofen, but if that doesn't work then a short course of prednisone is oftentimes very helpful. And needless to say, if you had such a severe reaction to nilotinib, then it's really not a medication that you can go back on.

Ms. Figueroa-Rivera:

Thank you. And the next question, Romelo is asking, other than monitoring lab work, what precautionary steps could be taken by those on TKIs to assist with preventing some of these short and long-term symptoms?

Dr. Hobbs:

Great question. So one of the common questions that I get is, am I considered immunosuppressed? And that was so relevant during COVID, people wanted to understand their risk, etc. Generally speaking, because most patients that are treated for CML are in remission, I generally tell patients that they're not at any increased risk for infections.

Now these medications can have long-term issues or side effects, including like for example, some of the medications can worsen cardiovascular comorbidities like diabetes or peripheral vascular disease or cardiovascular disease, and so I think really an important preventative measure is to try to talk to your doctor, and it may not necessarily be something that your oncologist alone can help with or something that maybe your primary care doctor can help you with, but managing things like high blood pressure, diabetes, high cholesterol, obesity, all those things are super important. Not smoking, not drinking in excess, are very important towards, not just generally speaking like a healthy life, but important especially in the context of taking medications that may have long-term side effects.

Ms. Figueroa-Rivera:

Thank you. And we'll take the next question from our telephone audience, please.

Operator:

Thank you. The next question comes from Laura. Laura, go ahead.

Laura:

Hi, thank you so much. My question is... all the research and studies that's being done on CML, is that also including children and teenagers or is it mostly just catered for adults?

Dr. Hobbs:

Great question, Laura. So, because CML is less common in children, the majority of studies in CML are done in adults but there is progress in CML for children. I think bosutinib was just approved for pediatric patients as well. So there is progress there as well. But, yes, the majority of studies in CML are in adults.

Ms. Figueroa-Rivera:

Thank you. And our next question comes from Joyce. Joyce is asking, what connections to other types of leukemia and family history are being evaluated? My family has a history of prolymphocytic leukemia, non-Hodgkin lymphoma, and chronic lymphocytic leukemia. I was told my CML was not related but having a hard time believing there's no connection at all, even if indirect.

Dr. Hobbs:

Great question and I wish I had a good answer for that. And so sometimes it can be environmental. There're certain areas of the country where we know there's higher likelihood of having a malignancy if there's some environmental exposure, and so that would make sense in a family. But we also know that there are lots of families like yours, you're not alone, where there is a variety of different blood cancers. And like you said, it's hard to think that they're unrelated.

So, there is definitely lots of research being done to understand genetic predispositions to these cancers, and I know that we're going to probably have more answers for that in the future.

For now, a common question that I get is, should I go test my children, for example. And the answer, at least today, is no because there's nothing that we're going to do preemptively or nothing that we can test for in advance. But, if you have the option of participating in a biobank or a tissue repository at your center, same with your family members, then that could probably help researchers to try to figure out, are there some genes that run in families that predispose them to having these different types of cancers?

Ms. Figueroa-Rivera:

Thank you. And our next question comes from our telephone audience, please?

Operator:

Thank you. Michael, your line is open, go ahead.

Michael:

Yeah, I had a question regarding the impact of sugar in clearing the tyrosine kinase as a receptor if activated by insulin.

Ms. Figueroa-Rivera:

So asking about sugar intake?

Dr. Hobbs:

Good question.

Michael:

Yeah, sugar increases your insulin.

Dr. Hobbs:

So, yes, sugar definitely will increase your insulin. Sugar levels in general do not interfere or interact with the tyrosine kinase inhibitors. And so they won't impact the success of treatment. Now generally speaking, I think we can all do with having less processed sugars and trying to avoid unhealthy sugars in our diet. That doesn't mean that you can't have sugars, especially if they're coming from healthy sources like whole grains or whole fruits.

Ms. Figueroa-Rivera:

Thank you for the question. The next question, Stacy's asking, when should therapy dosage be reduced if stable and undetectable for 2 plus years? My hair is falling [out] and my fatigue is atrocious and my doctor is hesitant to change therapy.

Dr. Hobbs:

Good question. I'm glad you asked it. And so, it sounds like the time is now. And the time is now to consider 2 different things. One is, what medication are you on and can you be on a lower dose, and I would say the answer is yes, you can be on a lower dose if in fact you've been in a deep remission or a stable remission for several years. And it will most likely help the hair and the fatigue. And then the next question to ask is, do you meet criteria for a treatment-free remission? And if that's the case then maybe you don't even need to lower the dose and you can just stop the medication altogether. Good luck.

Ms. Figueroa-Rivera:

Thank you. And we'll take the next question from the telephone audience, please.

Operator:

Thank you. Julia, your line is open, go ahead.

Julia:

Yes, having been a patient where I have actually had to have 2 infusions and I'm currently on the new medication called Scemblix®. It started less than about 2 months ago. What is normally you might expect a likelihood of this fluid retention to occur with this possible medication?

Dr. Hobbs:

Great question. And so it's really not something that's reported with Scemblix. I'm sure there will be some case report or something like that, but it's really not a side effect that we see with asciminib. So hopefully for you, you won't have that again.

Ms. Figueroa-Rivera:

Thank you. And our next question, Mary is asking, I've been in treatment-free remission for almost 2 years. Does that mean I might be cured?

Dr. Hobbs:

Good question. Yes, it does mean you might be cured, but we really hesitate to use that and we know from some studies that have followed patients for many years, obviously the numbers are small, but maybe like 10% to 15% of patients can have a later recurrence. And so, I would say enjoy being off of medication but certainly it's possible that it would come back. Certainly the longer you're off of it, the lower the likelihood, but we really do hesitate to use the word cure.

Ms. Figueroa-Rivera:

Thank you. Thank you, Mary, for that question. Doctor, a lot of people are asking about the word "cure" for CML, if we are reaching a point where we could utilize that term? Is there anything on the horizon that you're excited about now in regard to CML and pushing towards that cure?

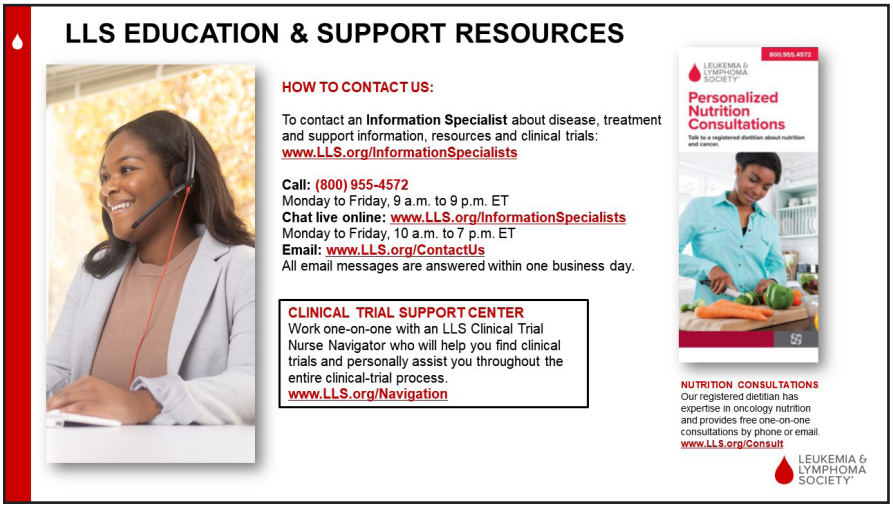
Dr. Hobbs:

Good question and I think we have to really think about what do we mean when we say cure. And I think one of the things maybe with the question I just got was, can I live without treatment indefinitely, and I guess that's one way of defining cure. But I think that when I look at charts that show that patients with CML have a normal life expectancy, that's almost just as good as a cure, as long as patients are being well managed and the doses of the medications are adjusted to make sure that patients live well, because many of my patients live with CML without a lot of side effects. And so, for those patients taking the pill ends up being less of a big deal.

Now, of course, it would be wonderful if we could have more patients in treatment-free remission indefinitely, to really get it to what we would all kind of associate more traditionally with the word "cure". And so, some of those studies that I was talking about at the end, combining different medications with the goal of trying to deepen those remissions and help people to stay off therapy, I think have a lot of promise. For example, the studies that are combining 2 different medications like asciminib and imatinib.

Ms. Figueroa-Rivera:

Thank you. Thank you so much, Dr. Hobbs, for really volunteering your time and providing us with your expertise today.



Slide 32: LLS EDUCATION & SUPPORT RESOURCES

Now, if we were not able to get to your question today or you want information or resources, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, or you can reach us by email at LLS.org/ContactUs. You may also reach out to one of our Clinical Trial Nurse Navigators in our Clinical Trial Support Center by visiting LLS.org/Navigation or call an Information Specialist in regard to finding a clinical trial.

Slide 33: LLS EDUCATION & SUPPORT RESOURCES

The Leukemia & Lymphoma Society offers financial assistance to help individuals with blood cancer, as we heard Dr. Hobbs speak about the costs for CML, we would definitely like to assist you. You can visit our website at LLS.org/Finances for more information or contact an Information Specialist.

Slide 34: LLS EDUCATION & SUPPORT RESOURCES

The Leukemia & Lymphoma Society is also a proud partner with Dollar For, a national nonprofit organization that helps patients apply for hospital debt forgiveness and eliminate medical bills. Their services are completely free and you can visit LLS.org/DollarFor for more information.

Dr. Hobbs, thank you again for volunteering your time with us today and on behalf of The Leukemia & Lymphoma Society, thank you all for joining us.

Goodbye and we wish you well.