Carrie Callas (00:06):

Hello and good afternoon to everyone on the call. Thank you for joining us today for our Leukemia Q&A. Today's program is focused on chronic leukemias. My name is Carrie Callas. I am the Director of programs at the Leukemia Research Foundation. I'd like to take an opportunity to thank our webinar partner, Patient Empowerment Network and our program supporters, AbbVie, BeiGene, GlaxoSmithKline, and Merck.

(00:36):

The Leukemia Research Foundation's mission is to cure leukemia by funding innovative research and to support patients and families. The Foundation has raised over $83 million in support of its mission and has funded research grants to over 600 new investigators worldwide. Our free support programs for leukemia patients and their loved ones include information and resources, educational programs like this one, peer support services, financial assistance, and a directory of other helpful organizations and resources.

(01:24):

[Participant instructions omitted]

(02:10):

We are incredibly grateful to have our expert panel here today. Dr. Deininger from Versiti and the Medical College of Wisconsin, Dr. Kittai, from the Ohio State University, and Dr. Thirman from the University of Chicago.

(02:26):

I would like to now introduce our moderator of today's program, Dr. Karen Carlson. Dr. Carlson is Assistant Professor of Medicine at the Medical College of Wisconsin, Division of Hematology and Oncology, specializing in acute and chronic myeloid leukemia, adolescent and young adult leukemia, myelodysplastic syndromes and myeloproliferative disorders. Dr. Carlson's basic and clinical research focuses on bone marrow microenvironment and its impact on normal and leukemic blood cell production.

(03:00):

I will now turn it over to you, Dr. Carlson.

Karen Carlson (03:03):

Oh, thank you so much, Carrie. I'm so grateful to be able to moderate this session. And just briefly before we start, I was hoping each of our panelists could briefly introduce themselves as well. Dr. Thirman, would you be able to give us just a few bits of information about yourself and your expertise?

Michael Thirman (03:23):

Yes, so I'm Michael Thirman. I'm at the University of Chicago. I have a lab here that studies leukemia and in particular fusion genes in leukemia. And in the clinic I take care of patients with CLL, CML, AML, MDS and other blood cancers. I've been fortunate to be involved with the Leukemia Research Foundation for a long time. I received a Young Investigator award from them at the start of my career and served as the chair of the Medical Advisory Board for a few years. So very grateful to the LRF for the work that they do.

Karen Carlson (04:06):

Thank you. Dr. Kittai, could you introduce yourself?

Adam Kittai (04:09):

Hey, Adam Kittai. I'm an assistant professor at the Ohio State University. I'm a clinical investigator and I specifically study chronic lymphocytic leukemia and Richter's Transformation. My clinic is all CLL all the time, so I like CLL a lot and I'm happy to be here to answer any questions you guys have.

Karen Carlson (04:29):

Awesome, thanks. And Dr. Deininger, would you be able to introduce yourself briefly?

Michael Deininger (04:36):

I'm Mike Deininger. I'm the Director of the Versiti Blood Research Institute in Milwaukee, Wisconsin, and a Professor of Medicine at the Medical College of Wisconsin with a longstanding interest in really chronic myeloid leukemia and myeloproliferative disorders [inaudible 00:04:55] lab and been involved in clinical trials and CML [inaudible 00:05:02]. I look forward to your questions and thank you for having me.

Karen Carlson (05:08):

Wonderful. Well, thanks for introducing yourselves and we'll go ahead and get started. So Carrie and I tried to pull the questions together to make sure we could talk about some consistent themes and the first theme that came up were questions about treatment and there were several questions specifically about CLL and the role of watching and waiting for people who have stage zero CLL. I guess specifically how long can this watch and wait period last? Is it a 10 years hard and fast or is there some gradation there. Dr. Kittai?

Adam Kittai (05:47):

Yeah, that's a great question. So how I counsel my patients is that it can be many, many years from the time of diagnosis until we need to start treatment. And many of my patients describe this as not watching and wait but watch and worry because they're just sitting around and worrying about their disease when we're not doing much about it.

(06:04):

And the reason why we don't treat early is that there was historical data using chemo immunotherapy that showed that if we treated earlier without waiting for the indications to treat that we use for CLL, that patients didn't live any longer and actually they lived less long because they had all the side effects from the chemotherapy. That paradigm is now being reexamined in a couple of different clinical trials with our new drugs and so we're excited to see where that goes. But how I usually tell my patients is that there was a recent study that looked at three prognostic factors that could help predict when time to first treatment is.

(06:43):

One of those is, if I can feel lymphadenopathy, whether they have the IGHV-unmutated status or if their lymphocyte count was greater than 15. If you have none of those factors, the study showed that patients could be in watch and wait for five plus years. If you have one of those factors, it's still around five plus years. Two, it's three plus years and all three is two plus years.

(07:08):

And these are all averages, but it helps give my patients a good idea of what to expect. And then there was a recent study that was published by the European group that looked at thousands of patients in watch and wait. And what they found was that if you lacked a TP53 mutation and also you had IGHV mutated status, that the median time to first treatment was 10 years. Actually 10 plus years.

(07:35):

So I look at all those different things and we discuss it with our patients and let them know what to expect. And it's totally a time when a lot of patients do worry more about their disease where we're just watching the numbers rise without treating it.

Karen Carlson (07:48):

Another individual wrote in asking whether CLL can turn into a different type of lymphoma, even if it's during the watch and wait period. And I guess an additional question, if that were to happen, what would that look like?

Adam Kittai (08:07):

I'll go ahead and keep talking.

Karen Carlson (08:08):

Yeah, thanks Dr. Kittai.

Adam Kittai (08:08):

So when CLL transforms into an aggressive lymphoma, that's called Richter's Transformation and that's probably what they're referring to. It happens in anywhere from one to 10% of patients and typically it happens when patients are actively progressing and they start new treatment. So it can happen during the watch and wait phase, but it's not so typical. Usually we see it when patients start a treatment and the reason why we see it then is because they probably had that Richter's Transformation occur and that's why they started to not feel well and while they met indications to treat.

(08:47):

And so typically, I see that transformation occur when treatment is initiated and Richter's Transformation is an area of unmet need in the world of CLL, and there are new studies that are coming out that look really promising for Richter's Transformation. But overall Richter's Transformation is one of those events that I would advise someone to get a second opinion at an academic center if they're not already being seen at an academic center because it is a very difficult disease to treat.

(09:20):

I think I hit all the questions, but I think there might have been one more.

Karen Carlson (09:22):

I think so. Thank you. That was perfect. Dr. Thirman, I'll throw this one your way. If someone is in watch and wait for their CLL, are there precautions that you would advise for someone who was going to take a trip overseas?

Michael Thirman (09:39):

Well-

Karen Carlson (09:39):

Or anywhere?

Michael Thirman (09:40):

Yes. That's a good question. So usually there are very few precautions for people who are in watch and wait. I do think that people with CLL are at higher risk of infections, so I would counsel certainly when on an airplane or going out that it would be advisable to wear a mask as much as possible. I think it's important to make sure that you're up-to-date on your COVID shots and the booster. But other than that, I think most people in watch and wait are able to do most things without restrictions.

Karen Carlson (10:23):

Wonderful. I may take a lead from your mention of being up-to-date on vaccinations and segue a little bit to COVID and chronic leukemias. And I guess I'll send this back to Dr. Thirman again. What do you recommend in terms of booster vaccinations? Or anyone who would like to answer. Especially, do you recommend a second bivalent COVID vaccine?

Michael Thirman (10:51):

Well, that's a good question. I recommend that everyone receive the first bivalent booster and it looks like the recommendation is going to be yearly in terms of getting a second bivalent booster shot. That's still a little bit in flux. I also would say that for people with CLL, that if they do test positive for COVID, in general I recommend that they take Paxlovid, except if they're on medications that have drug reactions. So that's something that you need to check with your provider. Sometimes a drug can be held for a few days, other times not. But in general, we try to make sure that everybody with CLL gets treated and also of course vaccinated.

Karen Carlson (11:51):

Do you worry that the vaccine could make the leukemia worsen or relapse?

Michael Thirman (11:56):

Not at all. I don't think there's any reason to think that there's any risk at all from the COVID vaccine in terms of relapse or progression. I think there are people out there who've tried to scare people about the COVID vaccine and I think that's very unfortunate.

Adam Kittai (12:15):

One thing to remember is that if you have CLL and you get the vaccine, it is normal to develop lymph nodes on the side that the patient got the vaccine, which can be very scary for our CLL patients because they'll think that their disease is progressing. But it will go down. The lymph nodes do typically go down after the vaccine. There is no concern that'll make the lymphoma or the CLL get worse.

(12:41):

And the other point there too is that whenever one of our CLL patients get an infection, they have more white blood cells than a normal person. So we do typically see the white blood cell count go up and then come back down after an infection or even potentially a vaccination. And that's just because you just have more white blood cells in your system, so that's why you react that way. So if you do get the

vaccine and your lymph nodes do increase on the side of the vaccine, they should get better, but certainly consult with your doctor as well.

Karen Carlson (13:12):

Awesome, thank you. I'm going to pivot a little bit now to some very specific treatment questions and I'm going to start with a question for Dr. Deininger. Someone astutely wrote in asking whether asciminib will be a frontline therapy for CML anytime soon. What are your thoughts about this?

Michael Deininger (13:32):

Question is anytime soon? I will say probably not. If the question is at some point in the future, then I would think absolutely, yes. So there are studies ongoing as we speak. I think it's safe to assume that these studies will show that it's highly efficacious as well [inaudible 00:13:53] agents, but these trials just have to run their course until the company can make an application for approval. So how far that's out? Always [inaudible 00:14:04] a couple of years. Two to three years, perhaps.

Karen Carlson (14:12):

Got it. Thank you. In terms of CML, are there other new therapies that patients should be aware of?

Michael Deininger (14:19):

There are several other new [inaudible 00:14:26] that are seeking regulatory approval. I do not personally think that they will really change the game here because there are more [inaudible 00:14:38] drugs that will not really add to the [inaudible 00:14:44]. We'll have to see where it goes. Some of the data are still immature, so maybe there's a positive surprise here and there, but we'll what we'll have to see. So I don't think anything fundamentally different is on the way at this point.

Karen Carlson (15:00):

All right. Thank you. A similar question for Dr. Kittai. Are there new therapies coming down the line soon for CLL?

Adam Kittai (15:14):

Yeah, I think one of the most promising therapies that we're all excited about is a drug called pirtobrutinib. So right now one of the main drug classes that we use to treat CLL are something called the BTK inhibitors and that's ibrutinib acalabrutinib and then recently approved zanubrutinib. And we consider ibrutinib the first iteration of the BTK inhibitors and then acalabrutinib and zanubrutinib as the second generation BTK inhibitors. Acalabrutinib and zanubrutinib are both safer than ibrutinib. And now we have a new drug that just got approved for mantle cell lymphoma called pirtobrutinib which also targets that same protein, the BTK protein.

(15:58):

And it works in a way that it binds slightly different than the first and second generation BTK inhibitors. So it was developed specifically for patients who are refractory to those first and second generation BTK inhibitors. And the reason why I say I'm excited about this drug is not only will it work for patients who have progression on one of those first or second generation BTK inhibitors, it also looked like it was remarkably safe in a very large trial.

(16:25):

And so I think that drug specifically will allow us to treat patients with BTK inhibitors for an even longer amount of time and given the safety profile, I think that's why I'm really excited about it.

Karen Carlson (16:36):

Oh, that makes sense. I guess a question I'll throw towards Dr. Thirman. How does the presence of a TP53 or a deletion 17P impact your choice of treatment for CLL?

Michael Thirman (16:52):

Well, that's a good question. It used to be that would help determine whether or not someone would respond well to chemotherapy. With the newer drugs that we have, the BTK inhibitors that Dr. Kittai was just talking about in venetoclax, that's less of an issue. In general, the TP53 or deletion 17P mutations are thought to confer a higher risk for progression, but the patients who have these mutations are still responding very, very well to the new therapies that we have in CLL.

Karen Carlson (17:33):

Oh, wonderful. I guess for either of our three participants, we had an individual write in who had been undergoing treatment or has had a diagnosis of CLL for many years and back in the age of FCR and they've moved through several other therapies including ibrutinib and venetoclax. I guess the question is what are next? And I appreciate we're not going to render treatment decisions for an individual, but certainly thoughts for people who may be in a similar position. What would be your armament for next choices for them?

Adam Kittai (18:15):

I can take this one. So I think if someone has already relapsed after both a BTK inhibitor as well as venetoclax they certainly should get a second opinion at an academic center. So in terms of simply drugs that you can use, unfortunately there's not much out there that really works in this scenario. There are a couple of things that can be done, but most of them are off-label. So I have combined BTK inhibitors and venetoclax for these patients and recaptured responses. So combining ibrutinib, acalabrutinib or zanubrutinib with the venetoclax seems to work. Ultimately though, they likely need to be considered for a stem cell transplant at this point, which is an option. But certainly there's a lot of clinical trials options out there if they can get connected.

(19:07):

That drug that I just talked about, pirtobrutinib is now approved for mantle cell lymphoma. So oftentimes, when a drug is already approved for another indication, you can apply for off-label use, especially with the amount of data that supports pirtobrutinib with CLL. I can imagine that you could get it as off-label use in this scenario as well. And then there are other options for clinical trials in CAR T-cell therapy for patients who have progressed on both those agents.

(19:34):

And lastly, the last drug class that could potentially be used are something called the PI3 kinase inhibitors, but recently it's hard to access those drugs because there was a meeting at the FDA where they took most of them off the market. But you still probably could get a drug called idelalisib if you wanted to. But that drug also hasn't been very well tested in patients who have already received the primary therapies, the BTK inhibitors and the BCL2 inhibitors.

(20:01):

So in summary, I think that patients who are progressing on both those drugs should definitely be seen at an academic center to consider a clinical trial. And if not, I would probably combine the two. But obviously these conversations need to occur with their local provider as well.

Karen Carlson (20:18):

And it sounds like an additional evaluation for any lymph node that may be changing in character suggesting fundamental changes in the disease course as well might be useful. Again, at an academic center like you suggested earlier.

Adam Kittai (20:31):

Yeah, so if somebody is progressing with lymphadenopathy alone, meaning their lymph nodes are getting bigger without an elevated white count, something I get concerned about is did they transform to Richter's Transformation like we talked about before? And that is treated much differently than CLL. And so if there's a concern that someone has Richter's Transformation because they have big lymph nodes, they're having terrible symptoms, they definitely should be evaluated and get a biopsy to look to see if that has occurred or not.

Karen Carlson (20:59):

Oh, thank you. I guess I'll throw this out to all three of you. In terms of side effects now for some of the CLL therapies or actually CLL therapies that may be used in other malignancies as well. Low platelet counts, low neutrophil counts, anemia, is that something that can be expected either at the beginning or long term with people treated with venetaclax?

(21:31):

Dr. Thirman, would you like to take that one?

Michael Thirman (21:33):

Sure. We do see low blood counts not uncommonly with venetoclax. Usually the counts are not severely low, just mildly low and that's something that people can usually tolerate. Sometimes, if either the platelet count or the neutrophil count is very, very low, we can reduce the dose of venetoclax. It's also important to look and see if there are any other drugs that are affecting the metabolism of venetoclax. So sometimes some antifungals can affect the dose that should be used, so that's important to keep in mind. So again, it depends on the individual situation and it's hard to know without seeing what someone's been treated with and what their blood counts are to make a specific recommendation, but those are the general ways I look at it.

Karen Carlson (22:30):

Oh, thank you very much. And same thing, anyone who'd like to comment on this next question. Is ibrutinib safe for people who are on anticoagulation? I know there's a lot of people who may be on blood thinners for a blood clot or even a very common condition called atrial fibrillation. Is this a safe combination?

Adam Kittai (22:52):

So we do not give BTK inhibitors with warfarin, so it's actually contraindicated to do. Anything else but warfarin is okay. However, I do get worried as patients add on anticoagulates. So for instance, if someone has a heart attack and is on an antiplatelet plus Plavix plus a DOAC or something like that; and

a DOAC, I mean a direct oral anticoagulant in apixaban or rivaroxaban and they're also on ibrutinib or another BTK inhibitor, that's what starts to get me a little bit worried when they're on multiple different drugs that can lead to bleeding.

(23:30):

That being said, I have done it. It's not a reason to stop it, especially if they're going to be on these blood thinners for a time limited situation. So it really depends on patient to patient. But I would say that surely no warfarin for sure with the BDK inhibitors, but if someone is just on apixaban or rivaroxaban for their atrial fibrillation, I've done that a lot.

Karen Carlson (23:53):

If someone started to experience bleeding problems, say they had blood blisters start to crop up in their mouth or their skin or nose bleeds, would that be a signal to go back and speak to their doctor for some more advice?

Adam Kittai (24:07):

100%.

Karen Carlson (24:08):

Awesome, thank you. All right. I'm going to move next to another form of treatment being hematopoietic cell transplantation. We had several questions, one of which was specific to CML and I may throw this to Dr. Deininger. Is there a point after an allogeneic stem cell transplant or cell transplantation in which patients no longer need to be tracked or have blood work to monitor for their CML to relapse?

Michael Deininger (24:43):

Well, that's a really good question. I would answer it depends on in which state of disease the transplant was done when this was very high risk situation. Say transplant in our second chronic phase after plastic transformation, then I would think it is wise to monitor [inaudible 00:25:11] long term just to pick up an early relapse, which actually has been described up to 80 years post-transplant. On the other hand, a transplant versus [inaudible 00:25:25] chronic phase maybe failed one [inaudible 00:25:33] required. I think it's [inaudible 00:25:46] that the risk will never be zero, but there is nothing without any risks that we do ever in life. So I would support that maybe up to five, six years I would think it could be done.

Karen Carlson (26:01):

Got it. But certainly it sounds like someone should anticipate maintaining regular blood work with their transplant center who cannot just monitor their BCR-ABL but maybe monitor chimeras and things like that as well, especially during those early transplant years for CML.

Michael Deininger (26:18):

I'm not sure. I think if you have a successful [inaudible 00:26:22] stem cell transplant, you [inaudible 00:26:27] immunosuppression that you have no signs of [inaudible 00:26:32] disease, you're just fine. I think at some point you can actually go back to your primary care provider and [inaudible 00:26:43].

Karen Carlson (26:42):

Wonderful. Thank you. For any of the three of you, what are some good resources for learning about transplants? Specifically if someone wanted to find out about success rate at a specific center and what to expect overall for life expectancy improvement after a stem cell transplant? Dr. Thirman? [inaudible 00:27:06].

Michael Thirman (27:06):

Well, our transplant group has put together a handbook that we give to patients when they come the first time as a list of all the questions that people have asked us over the years and the answers that we've put together in general. Not for someone's specific disease but for transplant in general, what to expect. And I think a lot of the transplant centers have that. I think there's material online from the Leukemia Research Foundation and other societies also about transplant. Probably the best thing is to go around to one or two transplant centers and meet with the team and see what information they can provide and what resources they have.

Karen Carlson (27:57):

And I'll add to that, that bethematch.org is often a very good resource as well. It's through the National Marrow Donor Program or NMDP. And while they may not have information, as Dr. Thirman alluded to specifically relevant to an individual's particular disease and donor options, it's a great reference for transplant quality around the country.

(28:26):

Another question about transplant. What donor options are available for someone who may not have siblings or may not have a parent who is available to be a donor?

Michael Deininger (28:41):

I'll take that.

Karen Carlson (28:46):

Yeah, awesome.

Michael Deininger (28:50):

In principle there's always the option of [inaudible 00:28:50]. It depends very much of what your ethnic background is, what kind of probability there is that you will find a good [inaudible 00:29:01] an acceptable match in one of the registries. Yeah, so that's certainly the first place to go to. In the past there has been a lot of interest in using donor [inaudible 00:29:20] as donor, which can be [inaudible 00:29:24] almost any situation. Now that usage has been declining recently [inaudible 00:29:30] or if [inaudible 00:29:35] qualifying for [inaudible 00:29:40]. But there are still some centers that will do [inaudible 00:29:43] transplants. So I think with that in mind, it's [inaudible 00:29:50] an option in practically everyone.

Karen Carlson (29:54):

Wonderful. So your sound cut in and out, but just to briefly synopsis, matched unrelated donors are options for people as well as umbilical cord transplants and also haploidentical transplants, depending on who's available from a family member. Awesome, thank you so much.

(30:19):

And then I think the final group of questions in our bucket of treatment options really circles around clinical trials, and I know we've alluded to that a few times. We had people ask how do they enroll in a clinical trial? Dr. Kittai, are you able to field that one?

Adam Kittai (30:35):

Yeah, sure. So clinical trials are typically offered at academic centers or centers that are associated with academic centers. There are also some large groups out there that have the capability of doing clinical trials such as a group called Sarah Cannon basically in Southern United States. So clinical trials are available in a lot of different places and ultimately what you should do is inquire with your treating physician about clinical trials, whether they have them available at wherever you're being seen. And it's always a good question to ask, "If you don't have any clinical trials, is this a situation where you think me looking for a clinical trial is worthwhile?" And your local doc should be able to give you an idea of whether or not they think that a clinical trial is a good idea for you.

(31:27):

Typically, most academic centers will have the list of clinical trials somewhere on their website if you just look and dig deep into it. You can also look@clinicaltrials.gov. It's a hard website to navigate to be honest, but you can try inputting your disease type into the search bar and doing a search that way to try to find clinical trials across the country. And you can also sort them by whether or not they're actively recruiting patients or not and then try to reach out to whoever they have listed there as the primary investigator for the clinical trial.

(32:00):

But there's all sorts of clinical trials. I think start with your treating provider first to determine whether or not you are somebody that he or she thinks should be on a clinical trial. And if you want to see what clinical trials are out there, you can try clinicaltrials.gov. But as I said, the website's a little bit wonky, so I would try maybe your local academic center, whatever's closest to you to see if there's clinical trials in your disease type.

Karen Carlson (32:23):

Wonderful, thank you. We had one very specific question asking about MR-1 restricted MAIT cells as an off the shell Allo CAR T-cell option. And I guess I may phrase that for people who are involved or interested in CAR-T as a therapy, what does the landscape look like for off-the-shelf CAR-T products versus CAR-T where it's made from a patient's own individual T cells? How far out is that?

Adam Kittai (33:00):

I can do it.

Karen Carlson (33:01):

Awesome. Thanks Dr. Kittai.

Adam Kittai (33:04):

So right now there is no approved off the shelf CAR T-cells. So as Dr. Carlson had said, CAR T-cells can either come from yourself or from someone else. If they are from yourself, that's called an autologous CAR T-cell product, versus someone else's called an allogeneic CAR T-cell product. And that's the same thing for stem cell transplant. It's the same language.

(33:31):

And right now, the way that CAR T-cells work is that they hook patients to a machine that takes out their white blood cells. They then modify those white blood cells in the lab to target the cancer and then they reinfuse those CAR T-cells back into the patient. Currently, CAR T-cell approvals using that method are approved for diffuse large B-cell lymphoma, follicular lymphoma as well as multiple myeloma and also mantle cell lymphoma. There are some studies looking at one of those products called liso-cel or Lisocabtagene maraleucel for CLL and that hopefully will work, but we have to see what the clinical trial looks like in the randomized study.

(34:18):

Then I should say that in general, what I'm seeing a lot of as opposed to off-the-shelf CAR T-cells is actually increased manufacturing time. So one of the biggest problems with CAR T-cells currently is that from the time of taking the white blood cells out and manufacturing them to target the cancer, to putting them back into the patient, it takes around three to four weeks typically.

(34:40):

And what we're seeing now is there's a lot of new studies using those same kind of products that I just mentioned, but shortening that time, which is the biggest deal currently with CAR T-cells because if someone needs CAR T-cells waiting three to four weeks is a long time before they get that therapy. So right now I'm seeing a lot of shortening of that time with a lot of different products. So I expect actually that to come around maybe first before off the shelf CAR T-cells. But yes, there was some studies presented at our recent national convention called ASH, looking at off-the-shelf CAR T-cells as an option.

(35:14):

And I'll end by saying, because I know I talked a lot about this, is that there's another group of drugs called bispecific antibodies that work very similar to CAR T-cells and those are off the shelf products. And what that does is it's an antibody that brings the T-cells over to the cancer. So that's an off-the-shelf product currently that it will be approved soon for various different diseases.

Karen Carlson (35:39):

Wonderful, thank you. We had a couple questions ask about why do people get these cancers and what are the risk factors. So I might ask Dr. Deininger to first talk about risk factors for developing CML and Dr. Thirman, the same question about CLL. Dr. Deininger?

Michael Deininger (36:23):

[*Added after program due to live answer being inaudible*] The incidence of CML is equal across the globe, with a slight male preponderance. There is no familial risk factor that we know of. As far as environmental risk is concerned, exposure to ionizing radiation increases the risk. This is from studies in Japan, where the incidence of CML increased approximately 8 years after the atomic bomb explosions.

Karen Carlson (36:36):

[inaudible 00:36:37]. Got it.

Michael Deininger (36:49):

[inaudible 00:36:47]. But that's about it. Nothing else [inaudible 00:36:53].

Karen Carlson (36:53):

Wonderful, thank you. Dr. Thirman, is it hereditary versus environment versus yes for CLL?

Michael Thirman (37:00):

Well, it's a very complicated question and difficult to sort out. So we know that there are some families that have a higher predisposition to develop CLL and I've had several patients with CLL who have close relatives who also have CLL. We also see that there's a little bit of an increased frequency of other blood cancers like multiple myeloma in people who have CLL. So I think there probably is a familial predisposition. We don't know what genes might be responsible for that.

(37:41):

In terms of environmental exposures, it's been very hard to sort out. There have been some questions raised about pesticide exposures of various types or herbicides and whether or not they might increase the risk of CLL. It's very, very tough to know that but that that's been something that people have questioned. So we have some data on hereditary factors and some data on environmental factors as well.

Karen Carlson (38:14):

Wonderful, thank you. We had quite a few questions about monitoring remission and the question of minimal residual disease in CLL. Dr. Kittai, could you talk a little bit about what remission is in CLL and what role minimal residual disease plays in understanding that?

Adam Kittai (38:35):

Yeah, so for patients on long-term BTK inhibitor therapy, typically they get into what we call a partial response and some patients, about five to 10%, will get into a complete remission or complete response. And for patients with venetoclax; and I'll talk about what I mean by partial response and complete response in a second. For patients on Venetoclax who complete one year of therapy in the frontline setting or two years of therapy in the relapse setting, they typically get into a complete response and can also get into a place called undetectable minimal residual disease.

(39:18):

So what are the difference between those? It's very confusing. So the response criteria are determined by our society called the International Workshop of CLL, and they are pretty stringent criteria for how much [inaudible 00:39:32] CLL you detect in your blood as well as near bone marrow. It turns out in general that the deeper responses that people get, the longer they tend to stay on therapy. So if you're on a BTK inhibitor and you get into complete response, typically you have longer time on therapy in that response than patients with a partial response. That being said, I have a lot of patients who have sat at a partial response for years and done just fine.

(39:58):

In venetoclax, the story's a little bit different. So it appears that the deeper that you can get into what they call undetectable minimal residual disease; and I'll talk about a second about what I mean by deeper; also seems to relate to how long patients have until they progress. So the better response that patients have, they typically have a longer time until they progress.

(40:22):

So what is undetectable minimal residual disease? I feel like I think about this in terms of how much CLL can I detect? So partial response, you can detect some CLL in the blood or bone marrow. Complete response, you can't detect any CLL in the blood or the bone marrow using standard testing, something

called flow cytometry. Undetectable minimal residual disease is you can't detect any CLL in the blood or the bone marrow or using standard testing or advanced testing called clonoSEQ, is typically the test that we're using as approved for FDA. And that's a special type of testing that looks at the smallest amount of CLL in your bone marrow.

(41:05):

And so that's the difference between all those things. In general, the less that you can detect the CLL, the better, the longer time that patients have until progression. In general, I don't really use the MRD testing all that much to make treatment decisions. A situation where I would consider using it is somebody who is on time limited Venetoclax therapy either for one year in the frontline setting or two years in the relapse setting who is particularly high risk.

(41:36):

So they might have those features that we mentioned earlier like a TP53 mutation or a deletion 17P mutation, and they're really worried about coming off. That's somebody that I might use the MRD testing and if they're undetectable on the testing, then I would take them off. But in general, when I go down that pathway of treating someone with Venetoclax, I usually stick to the one year or two years.

(41:58):

This is a hot topic by the way. Not everyone shares that opinion and I'm sure if you asked 10 different CLL doctors what they do in that scenario, we might all give slightly different answers. But that's what I mean by partial response versus complete response versus undetectable minimal residual disease.

Karen Carlson (42:15):

So I guess it's fair to say that if someone is in remission from their CLL, it may not mean that their cancer is completely gone. It's-

Adam Kittai (42:23):

Yes. And so as you noted, I did not say the word remission there at all.

Karen Carlson (42:26):

Yeah.

Adam Kittai (42:27):

I sometimes use the word remission when we ... It depends on who I'm talking to and what we're talking about. Remission can be a lot of different things. Unfortunately still with CLL, it's not considered a curable disease. We're hopeful that patients who hit that undetectable minimal residual disease level of detection are cured, but we really need to follow these patients for a really long time. And I do suspect that some of them might be cured, but I think that's still a rarity. And so I try not to use the word remission. I try to use those words I had said before, the partial complete response, detection of undetectable minimal residual disease to help guide my patients and inform them of how long I think that they'll be in a time where their disease is really well-controlled.

Karen Carlson (43:16):

Thanks. No, that's a wonderful explanation. Thank you. And now we have an assortment of questions of different topics, some of which we've hit already, but some really interesting questions. One person

wrote in asking about whether supplements like zinc or vitamin D are helpful for chronic leukemia. Dr. Thirman, would you be able to comment on that?

Michael Thirman (43:43):

Yes, I'm not aware of any studies that have shown a benefit to supplements. I think a lot of people have this belief that there has to be some supplement that will help with their leukemia and unfortunately I just haven't seen any positive results along those lines. And I think sometimes people can get themselves into trouble. I've seen people take too much zinc and have some effects on their blood counts from that. And so I suggest that instead of spending the money on the supplements, I would donate that money to the Leukemia Research Foundation and allow for more research in the future because I think that would be much better. And I think the only thing that people get from these supplements typically are side effects.

Karen Carlson (44:43):

Yeah, I appreciate that information. Another individual asked about the cost of CLL drugs and I think we can all appreciate that the CLL drugs and frankly also the CML drugs can be cost prohibitive. Could either of you comment on any information about when these drugs might cost less or become generic or available by sources that are aren't quite so costly?

Adam Kittai (45:16):

I can go ahead and chat about that. It'll probably still be some time before even ibrutinib becomes generic and that's because a government regulation on cancer therapeutics basically linked in the time that they're required to go generic. We recently talked about what year it will go generic, and it was much longer than I realized it would be. To be honest, I forgot what year that is. Someone could look it up, that'd be great, but I just don't know off the head the top of my head.

(45:44):

But what will I will say is that there are a lot of medication assistance programs out there. A lot of foundations offer this. I believe the Leukemia Research Foundation also offers things like this as well as the drug companies themselves have a lot of programs available where they can get you free drug or drug that is significantly discounted. So there are a lot of things called vouchers, medication assistance programs, as I said, that you should look into for sure before just accepting the bill that you get from [inaudible 00:46:18] insurance. Especially for lower wage earners, there are very much available options out there for patients to get these drugs covered.

(46:27):

So make sure to exhaust all of your medication assistance program options before paying for any of these things.

Karen Carlson (46:34):

And do you think patients can be directed towards those from their oncologist's office?

Adam Kittai (46:41):

Yeah, so certain oncologist's office are more equipped to do this than others. I know at OSU we have an entire group that's dedicated to doing medication assistance. I'm sure they have that at U Chicago and Wisconsin as well. And so this is another reason why getting a second opinion does matter. So for

instance, I've had patients who have come to me from three hours away just because they can't afford the drug and then we get the drug covered underneath our own programs. And then typically, if I can't transfer that program to the local doc, what I'll do is I'll be the prescribing physician and I'll see that patient maybe every six months and let the local doc see them in-between for blood draws. So maybe I wouldn't see them as often as I would someone who I'm taking primary care of, but I do this a lot with some partnerships across Ohio and other states for patients, and if I can get the drug cheaper here at OSU. So that's certainly an option as well.

Karen Carlson (47:37):

Well, thanks. Another question someone wrote in and asked whether myeloproliferative neoplasms such as myelofibrosis are considered chronic leukemias.

Michael Deininger (47:52):

I guess you could consider [inaudible 00:47:56] traditionally [inaudible 00:47:57]. They are very-

Karen Carlson (48:00):

Oh, Dr. Deininger, it's a little tough to hear you. I apologize.

Michael Deininger (48:02):

Okay, so is it better now?

Karen Carlson (48:05):

Yeah.

Michael Deininger (48:07):

Okay. So I'm saying some of these [inaudible 00:48:09] have traditionally been given different names that don't sound like leukemia, but in essence they are very similar. It's just that the manifestations they take are maybe not very high white counts or low [inaudible 00:48:27], platelet counts than high white cell counts. But in principle, all these [inaudible 00:48:32] related to each other. They are coming out of the bone marrow where stem cells acquire mutations that essentially work like growth factors. They tell the cells to grow too fast and over time [inaudible 00:48:48].

Karen Carlson (48:49):

Ah, thank you. That's helpful clarification. I know it's confusing terminology and that's very helpful. I may turn a little bit to some of the questions in the Q&A box. A few of these we've already addressed. There was a question about MRD testing for someone with CLL and then there was another question about side effects of ibrutinib versus acalabrutinib. I think we touched on it a little bit. I guess specifically, does acalabrutinib have some of the bleeding risks and other side effects that ibrutinib has?

Adam Kittai (49:30):

Yeah, so there was a recent study called Elevate RR that compared ibrutinib to acalabrutinib and what they found; and this was for patients with high risk disease, so they had to have either deletion 17P or something called deletion 11Q. And the primary point of this trial was to determine if acalabrutinib was safer than ibrutinib. And it turned out it was. There was less risk of basically all the side effects; hypertension, atrial fibrillation, and bleeding. And so in general, this was a, in my opinion, practice

changing trial where unless I'm putting someone on a clinical trial where they'll receive ibrutinib, I use acalabrutinib or zanubrutinib as standard of care. And I think a lot of my colleagues do the same thing.

(50:14):

And so it's a very rare situation that I will put somebody on ibrutinib as standard of care. Maybe it's a cost thing like we talked about earlier where for some reason I can get ibrutinib for a cheaper cost or something like that. But unless they're going on a clinical trial, all things considered equal, because of elevate RR, and then the other study which compared zanubrutinib to ibrutinib, which is ALPINE which just came out, which also showed that zanubrutinib was safer than ibrutinib in a different population of patients. In general, I'm no longer using ibrutinib in frontline patients.

Karen Carlson (50:41):

Got it. And the individual who wrote in is a singer and they're specifically asking whether either of these medications could impact their ability to sing.

Adam Kittai (50:53):

Not that I've heard. And so typically we don't see things like change in ... So one of the things that we do see sometimes in clinical trials, which is a funny word, is dysgeusia, which means altered taste. So when someone has altered taste, I typically would think that they have dry mouth or something like that. I haven't seen anything like that with the BTK members in general.

Karen Carlson (51:15):

Oh, wonderful. Wonderful. Another question about whether a patient with CML should regularly wear a mask.

Michael Deininger (51:27):

For old practical purposes, you should just follow what a normal individual would do. There's no evidence that risk is increased for CML patients unless you have active disease [inaudible 00:51:44] accelerated [inaudible 00:51:44]. Otherwise, just follow what [inaudible 00:51:51].

Karen Carlson (51:51):

Got it. So for someone with CML whose disease is under control and who's in chronic phase, probably no extra precautions necessary above what's currently being recommended. But for someone with accelerated or blast phase disease, obviously going through different types of therapies that might be different. Dr. Thirman, what's your recommendation for people with CLL and mask wearing?

Michael Thirman (52:17):

Well, so people with CLL are at risk for getting viral infections, and I mentioned this before, so I do recommend that CLL patients wear a mask whenever they're exposed to other people and to try to limit contact. I know it's getting difficult as people have wanted to put COVID behind them, but I do think people with CLL have to be a little bit more cautious than others still. And as I mentioned before, make sure you get the booster and if you do develop symptoms of COVID, get tested right away and hopefully get treated with a drug like Paxlovid.

Karen Carlson (53:05):

If someone with CLL comes in contact with someone with COVID but does not themselves yet ... or I guess is not exposed, but kind of concerned about their risk of contracting COVID, is Evusheld something that is in the realm of options for someone with CLL?

Michael Thirman (53:28):

Well, that's a good question. Last year we were giving Evusheld to a large number of our CLL patients, but unfortunately it looks like the activity of Evusheld against the newer Omicron variants is very low. And so this is something that happens with COVID as it evolves over time. It doesn't look like there's much benefit to using Evusheld anymore. So we've pretty much stopped doing that. I don't know what they're doing at other centers.

(54:02):

But fortunately, Paxlovid still continues to work so if someone is exposed, they could just do a daily COVID test and if it's negative, they're fine and if it turns positive, then they could call their physician and try to go on Paxlovid, which still works against the Omicron variants.

Karen Carlson (54:22):

Wonderful. Dr. Kittai, it sounds like someone is very interested in your discussion of pirtobrutinib. I'm saying that all wrong. Do you have any thoughts about how long it may be before it's approved for CLL?

Adam Kittai (54:40):

That's a great question. I don't know. I hope soon, but I really have no clue.

Karen Carlson (54:51):

So we're not counting on days?

Adam Kittai (54:56):

No, but I'm hopeful maybe by the end of the year.

Karen Carlson (54:59):

Oh, wonderful.

Adam Kittai (54:59):

But I've said that before about other things and I've been wrong, so I try not to guess anymore.

Karen Carlson (55:06):

Understood. All right. I think we're making it through the questions. We had someone else write in who, it sounds like, is on a clinical trial. So they've been to an academic center and they're on a trial with ibrutinib and venetoclax. And again, not to give specific medical advice, but if someone were to have blood blisters while they're on ibrutinib in general or any signs of bleeding, would you recommend they give their treating doctor a call and that would be something that their doctor would want to hear about?

Adam Kittai (55:53):

Yes. And on top of that, when you're on a clinical trial, so any clinical trial has a protocol that's associated with it. And basically the protocol is this very large document, very dense, about a 100 to 150 pages sometimes that outlines basically every expected scenario that could happen on the protocol. And so there's usually some very specific warning, especially regarding bleeding and ibrutinib outlined in the protocol that the treating provider has to follow. So if you're having any bleeding events while receiving a BTK inhibitor, whether it be ibrutinib, acalabrutinib, and zanubrutinib, definitely get in touch with your treating doctor.

Karen Carlson (56:32):

Wonderful. Thank you. Carrie, I think we're coming near to the end of this session.

Carrie Callas (56:40):

Yes, thank you very much. So as we wrap up here, I just wanted to thank all of you; Dr. Kittai, Dr. Thirman, Dr. Deininger for being panelists and for letting us grill you with questions as well as giving up part of your Sunday for patients and caregivers. And Dr. Carlson, you did a fabulous job as our moderator, so thank you so much for that as well.

(57:07):

[Instructions for participants omitted.]

(58:07):

So thank you again to all of our fabulous expert physicians for giving of their time. We greatly appreciate it and have a great rest of your Sunday, everyone.

Karen Carlson (58:21):

Thanks.

Adam Kittai (58:22):

Thanks.

Michael Thirman (58:22):

Thank you very much. Take care. Good to see you.

Michael Deininger (58:28):

Thank you.