Carrie Callas (00:00:10):

Hello and good afternoon. Thank you for joining us for Leukemia Q&A. Today's program out of two programs is focused on acute 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 partners, Patient Empowerment Network, Know AML and Know ALL, as well as our program supporters, AbbVie, BeiGene, GlaxoSmithKline, and Merck. 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.

(00:01:04):

Our free support programs for leukemia patients and their loved ones include information and resources, education programs, peer support services, financial assistance, and a directory of other helpful organizations and resources. You can find out more at leukemiarf.org.

I also want to take just a moment to address one of the questions from our participants today about peer support and finding other patients and caregivers to connect with in your local area. Our Foundation has two partnerships: one is an online support community called the Leukemia Support Community, and we have a partnership with Imerman Angels for one-on one mentor relationships. We also have quite a few other opportunities available as well on our website, including My Leukemia Team, Cancer Buddy and others, so I will send in the email after today's program the recording links to those different resources that you can access for peer support.

(00:02:13):

[Participant instructions omitted.]

(00:02:58):

We're incredibly grateful to have our expert panel here today. We have Dr. Patel, Dr. Quigley, and our moderator is Dr. Carlson. Our panelists will introduce themselves in just a few moments, but to start, I would like to introduce our moderator, Dr. Carlson. Dr. Carlson is associate professor of medicine at the Medical College of Wisconsin, division of Hematology and Oncology, where she is the section head and medical director for acute care oncology. She specializes in acute and chronic myeloid leukemias, MDS, and MPNs. In addition to her clinical roles, Dr. Carlson is passionate about both patient and trainee education. She serves as an associate program director for the medicine residence at Medical College of Wisconsin. So I will turn it over to you, Dr. Carlson.

Dr. Karen Carlson (00:03:54):

Thanks so much, Carrie, for that kind introduction. I'm going to ask our panelists to unmute and turn on their video. And if we could start with Dr. Patel, could you just briefly introduce yourself to our listeners?

Dr. Anand Patel (00:04:13):

Yeah, absolutely. So hi, everyone. My name's Anand Patel. I am an assistant professor of medicine at the University of Chicago and a member of the leukemia and myeloid malignancy program there. I also serve as the medical director of our inpatient leukemia service, so very happy to be able to join you all this afternoon.

Dr. Karen Carlson (00:04:30):

Wonderful. And Dr. Quigley, could you give us a few sentences about yourself?

Dr. John Quigley (00:04:35):

Sure. Great to be here. My name is John Quigley. I'm a professor of medicine at University of Illinois Chicago, where I run the acute leukemia service here.

Dr. Karen Carlson (00:04:48):

Wonderful. Well, I want to thank all of our participants for submitting questions. They break down into a couple key areas. Treatments, prognosis, survival rates, causes and risk factors, side effects, remission and transplant, so we'll cover them in these big, general topics. And by treatment, I'll probably bridge from treatment right into transplant since those are related. So our first question pertains to a very common treatment these days for AML, and specifically two drug therapy with azacitidine and venetoclax. And one participant asked whether this combination is ever discontinued in a planned way in the course of therapy.

Dr. Anand Patel (00:05:45):

I'm happy to start. So I'll start by saying the combination of azacitidine and venetoclax has really become a very effective and standard way that we treat patients with a new diagnosis of AML that may not benefit as much from intensive chemotherapy, but as it's been studied in the context of clinical trials, it's thought of as being an indefinite treatment, meaning as long as it's effective and as long as there's not excess toxicity, cycles of it are given repeatedly. And sometimes there can be some adjustments to the dosing of the drugs, the schedule of the drugs being given, but overall, they're thought of as being indefinite.

(00:06:26):

In terms of data we have for treating patients for a set amount of time and then being able to stop that treatment, it's all what we call retrospective, meaning select centers have looked back at patients that may have had this happen for one reason or another and have found that some of those patients may indeed still have their leukemia stay in a remission despite stopping these therapies. That being said, this is a critical question in one that would likely require what we would call a prospective study, meaning we talk about the risks and benefits with the patient ahead of time and ideally, enroll them on something like a clinical trial that would be looking to exactly answer that very good question that was brought up, which is how much azacitidine-venetoclax? How many cycles are necessary once someone is in a remission?

Dr. Karen Carlson (00:07:18):

Dr. Patel, if someone had no evidence of an unfavorable mutation in their initial biopsy and they maintained that absence of unfavorable mutations several years into azacitidine and venetoclax therapy, would that change your recommendation at all?

Dr. Anand Patel (00:07:37):

That's a great question, and I think as you talk to different physicians that take care of patients with leukemia, you may get slightly different answers. I would still be leaning towards considering it an indefinite therapy, meaning I don't think my recommendation would be let's stop the azacitidine and venetoclax completely, particularly if there have not been significant toxicities such as frequent blood

transfusions or life-threatening infections. What may be adjusted over time though is how much of each drug is given.

(00:08:07):

So using venetoclax as an example, many times for the first few cycles of therapy, venetoclax may be given for three to four weeks even consecutively before being stopped. However, the longer someone's disease is in a remission, the more I think about cutting down the duration of that venetoclax and potentially allowing a patient to be off therapy in between cycles for slightly longer periods of time.

Dr. Karen Carlson (00:08:35):

Wonderful, thank you. Before we go further, I would like to turn the floor over to Dr. Perl and ask if he could give us a few sentence introduction. Welcome.

Dr. Alexander Perl (00:08:45):

Sorry for joining a few minutes late. I'm actually just dashing back from a prior engagement, so I really appreciate the flexibility here. So I'm Sasha Perl from the University of Pennsylvania. I've been a leukemia faculty member there for about 20 years. My focus there is on patients with acute myeloid leukemia. I do also see patients with ALL and some patients with MDS and CML, and my research interests have been in drugs that target oncogenic signaling such as FLT3 mutations on FLT3 inhibitors and other novel molecularly targeted agents.

Dr. Karen Carlson (00:09:17):

Thank you so much. We're so glad you're able to make it.

Dr. Alexander Perl (00:09:20):

Thanks for the invite.

Dr. Karen Carlson (00:09:21):

Oh, you bet. So I will go on to our next question, again in the treatment realm. So if someone has high risk AML that's described by the presence of an inversion three, monosomy seven and some of the MECOM and GATA2 transcription factor rearrangements, if they have relapsed disease... and this is getting a little bit specific so I'll preface the question by saying we're really not asking any of our speakers to give treatment recommendations, but rather to speculate just on general terms what they might think about next. So really, the question is for someone with high-risk disease who's relapsed after a bone marrow transplant, is there a role for: 1, clinical trial participation afterwards; or 2, therapies with things like T-cell infusions? Oh, Dr. Perl, we can't hear you, but thank you for taking that question.

Dr. Alexander Perl (00:10:38):

There. I just had to mute on my microphone, sorry. It's always a good time to think about a clinical trial option for relapsed AML. I sit on the NCCN panel and that's our frontline recommendation for anyone with relapsed disease in the absence of a targetable mutation where we think we have the right answer as to how to best to approach the problem. So in this unfortunate situation where you've gotten aggressive therapy frontline and despite that the leukemia is back, I do think that clinical trials are the best options for patients here. Outside of a trial or if you were looking for a particular kind of trial, I think often our goal is to stabilize disease with a goal of trying to get, again, immunotherapy to work in

ways that chemotherapy might not work, knowing that that can be associated with more durable responses or remissions over time. Whether that is with donor leukocyte infusions, whether that is with a second transplant or whether that's an interval therapy to set those kinds of treatments up, all of those are very reasonable things to do in this setting.

(00:11:39):

Recognizing what you said before, this is a very high-risk disease. This is very hard to treat and it's important to keep the feasibility of the trial or the feasibility of the therapy in mind in this setting. Not everybody's in a position where they can fly all over the country to get to a trial, so you have to keep the logistics in mind in this setting. It's aspirational to get on every study that's out there of every promising drug, but in reality, sometimes the things we have to balance that against are what's a reasonable thing to do given the distance you can go and still be under your physician's care or to get the transfusion support that you're set up for, or to stay with loved ones where you have support to get to and from visits. All of those things are really important to balance and there's no one right answer for everyone.

Dr. Karen Carlson (00:12:22):

Wow, thank you. That's very helpful information and a great perspective. Along those similar lines, but taking the transplant out of the equation. Really, those actionable mutations we think about are IDH1, IDH2, FLT3, what are the treatment options for someone who doesn't have one of those actionable mutations in their acute myeloid leukemia but has relapsed or refractory disease? Dr. Quigley?

Dr. John Quigley (00:12:56):

Hi. Sorry, excuse me. Just following on what Dr. Perl was just discussing, I think there are a number of new trials available at different institutions for relapsed refractory AML. I think the big discernment here is whether the patient has previously seen a drug called venetoclax or not. And so if patients have previously had intensive chemotherapy, generally we would go for the option of what's called a hypomethylating agent combined with venetoclax as probably the most likely option for this patient. We still have intensive chemotherapy options, as you know. High-dose Ara-C, mitoxantrone-based chemotherapies.

(00:13:48):

At our institution, we have a couple of trials for patients who been previously exposed to venetoclax where we combined it either with gemtuzumab or a drug called omacetaxine. But the point is that actually, compared to say 10 years ago, there's a big group of new therapies that are available. That's not even speaking about the anti-CD47 antibodies, the BiTE antibodies, et cetera. There's a large group of different trials available and a big choice in terms of therapies as opposed to previously, where we had very limited options for these patients.

Dr. Karen Carlson (00:14:28):

Understood. Thank you. There's a few questions about this idea of precision medicine and specific gene mutations being targeted and we alluded to IDH1, IDH2 and FLT3. How about some of the other common mutations RUNX1 or SRSF2. Really, I guess I'll broaden the question a little bit. Are there new treatment regimens, new use of old drugs or clinical trials that really focus in on the precise mutations that a patient has?

Dr. Anand Patel (00:15:06):

I'm happy to start with that question, and I think you can look at this question in two ways, which is do we have therapies that we think of as being mutation agnostic? Meaning they're not specified for a specific mutation, but then when we look at large number of patients that have received those therapies, we find particular mutations that may have more of a benefit. So using RUNX1 as an example, as we've looked at large number of patients that have received azacitidine and venetoclax, it seems like patients that have a RUNX1 mutation benefit from that therapy maybe more so than they would benefit with intensive chemotherapy. So that's a good example to keep in mind. Flipping it the other way, therapies that are novel that are under investigation that we think may help specific molecular subsets.

(00:15:58):

SRSF2 falls in a family of mutations that we call splicing or spliceosome mutations, and when you look at this family of mutations, they can actually make up a significant subset of patients with both AML and even MDS. So there's a family of drugs called IRAK4 inhibitors that are being investigated in this space. Dr. Quigley alluded to CD47 antibodies, and a specific CD47 antibody named Magrolimab is being looked at in disease with a TP53 mutation. So really, in this era of precision medicine, it's kind of a two-way street where you may be looking for drugs and specific mutations right off the bat, but you also may be looking at treatment regimens that are meant to treat AML broadly, but then as we learn more and gain more expertise with using these regimens, we may find out that patients with specific mutations may have a better response or may have a longer response or a more durable response than all-comers.

Dr. Karen Carlson (00:17:06):

Wonderful. So are you using these mutations to help pick the very initial therapy or are they more things that you're using after that initial therapy has been initiated to decide what comes next if the disease doesn't respond the way you hope it does?

Dr. Anand Patel (00:17:26):

Yeah, it's a great question. I would say at our institution, having the initial molecular information, meaning what mutations are there in someone's acute leukemia, right off the bat before treatment decisions are made is kind of our standard practice. So we have a panel of mutations that we send off and those come back in three to five days, and they tend to be what we call clinically actionable mutations, meaning mutations that we have a specific therapy in mind for. So there can be more extensive mutation panels that may even take a couple weeks to come back, but those oftentimes won't influence our initial treatment choice.

(00:18:04):

And nowadays, when it comes to AML specifically more so than ALL, we have several therapies that are approved for frontline use based on a specific mutation being present. So for example, the FLT3 mutation, intensive chemotherapy can be combined with an oral drug called midostaurin, and that's a standard treatment approach for FLT3 mutated AML. On the other hand, for patients with IDH1 mutations, a drug called ivosidenib. Particularly in patients that may not benefit from intensive chemotherapy, ivosidenib can be used alone as a monotherapy or it can be combined with azacitidine for patients with an IDH1 mutation. So certainly, even if you're not thinking about a clinical trial option, having that information in hand may actually significantly influence what your recommendation's going to be for the first therapy that someone receives for their leukemia.

Dr. Karen Carlson (00:19:03):

Oh, wonderful. That gives a lot of helpful insight for our viewers. Thank you. I hoped we could spend just a little more time talking about hypomethylating agents, and we have both the IV and now we have oral versions that are used in very specific circumstances. And one that someone wrote in to ask questions really about side effects of is a drug called Inqovi, and I think the question is really centered around is it ever safe to stop Inqovi? How do you manage toxicities like low platelet counts, anemia, infections? Any one of you all interested in tackling the question of Inqovi-associated side effects?

Dr. Alexander Perl (00:19:56):

I can dive in on that. Inqovi's a brand name for the oral formulation of decitabine it's given with a second drug called cedazuridine that improves its availability in terms of its absorption and essentially makes the drug equivalent in IV forms to the oral formulation in terms of the drug exposures that patients see. So treating a patient with IV decitabine or treating a patient with oral decitabine with cedazuridine, again called Inqovi, should be more or less the same in terms of the amount of drug exposure. Now, the tricky thing is if you're seeing toxicity with the IV formulation, you can just dial the dose down. Standard dose being say 20 milligrams per meter squared, we can go to 10 milligrams, we can give it less frequently, et cetera, but there's one pill size of Inqovi, so that makes it a little bit more challenging, but we can use our approach that we would use in general and maternal medicine.

(00:20:48):

If something is causing unexpected toxicity, the way we might decrease the overall delivered dose would be instead of giving the drug for five days in a row Monday through Friday, for example, you might give it Monday, Wednesday and Friday and consider that a full treatment. There are ways you could spread out the therapy so that instead of giving five treatment doses over four weeks and repeating every month, you might wait a little bit longer between cycles in order to let toxicities resolve. So there are some ways to work with this, but at present there's only one size of pill, so we don't have a way to cut it in half, cut it in quarters, et cetera, and assume that we're getting the same amount of medicine or a fraction of that to the patient. At present, that's the way we've been adjusting for toxicity, but that can be done. I've done that with my own patients.

Dr. John Quigley (00:21:36):

Sorry, can I just hop in there?

Dr. Karen Carlson (00:21:37):

Oh yeah.

Dr. John Quigley (00:21:39):

The other thing is that the oral medication seems to lot cause a lot more fatigue. Certainly if you look at the prescribing information, it says it basically doubles the fatigue of the IV. So it may be for this particular patient who I see I think was 87, it might be better to actually go back to the IV and as Dr. Perl was saying, reduce dose. But the IV form may cause less fatigue than the oral medication.

Dr. Anand Patel (00:22:11):

One other point I wanted to briefly add about Inqovi, particularly as I know many of the questions are geared towards patients with acute leukemias, I think it is important to note that Inqovi as of right now is approved for patients with myelodysplastic syndromes and CMML, or chronic myelomonocytic leukemia. There are ongoing trials to confirm that the use of Inqovi with venetoclax is equivalent to

using an IV form of a hypomethylating agent and venetoclax. So certainly in the future, we may be able to have an oral-oral regimen, so both medicines being oral and being able to treat patients with acute myeloid leukemia with an oral regimen, but that work is ongoing in the context of clinical trials right now.

Dr. Karen Carlson (00:23:02):

Wonderful, thank you. I'm going to jump over to some questions now about bone marrow transplantation. And just a general question, how successful have they been for individuals with AML and have there been improvements in success rates with transplants over the past five years? Dr. Quigley?

Dr. John Quigley (00:23:32):

Okay, thanks. So I think the major thing that's happened in transplant in the last couple of years has been really management of graft-versus-host disease and this idea of using post-infusion cyclophosphamide, and it really I think has a dramatic improvement in graft versus host disease rates. And what that is doing is reducing the unfortunate mortality that's associated with the disease, so I don't think we've made any big changes in our conditioning regimens to improve our outcomes. The outcomes remain the same about 50 to 60% overall survival at five years, but I think that the reduction in the graft-versus-host disease has allowed us to use a variety of different protocols and different conditioning regimens so now we can use myeloablative, reduced-intensity haplo-cord so almost everybody can find a donor, I think. And so in that way, I think that's improved our outcomes with this disease.

Dr. Karen Carlson (00:24:50):

Oh, you read my mind. Oh, go ahead Dr. Perl.

Dr. Alexander Perl (00:24:52):

One important expansion of that is even though it may seem like the outcomes aren't getting all that much greater in terms of overall survival, who we can transplant has dramatically expanded by this approach. And I think that's a real advantage of this advance in immunosuppression, as Dr. Quigley just mentioned, with post-transplant cyclophosphamide. This was a immunosuppression regimen that was developed at Hopkins specifically for haploidentical donors to provide essentially a more immunosuppressive and a particular immune suppression that would be appropriate for that population. Well, it turns out that has become the standard of care for those donors, and the outcomes with those identical transplants look very similar to what we see with either matched sibling or matched unrelated donor and actually were superior to cord transplants. So many, many more people are getting haploidentical transplants, which just gradually expands the donor pool.

(00:25:47):

And then recently, the BMT CTN presented data at ASH showing that in unrelated donor transplant, particularly in patients receiving unrelated donor transplants with reduced-intensity, the outcomes from those patients getting a post-transplant cyclophosphamide approach were superior to those using this previous standard approach for immunosuppression. So again, this is really taking over as our standard immunosuppression approach regardless of the donor, and this basically means that we don't have to worry really anywhere near as much about how well-matched a donor is and we're starting to look at

mismatched donors, is that going to be equivalent with this approach, et cetera. And just really, the whole question of can you find a donor for your patient is largely going away.

(00:26:32):

It's not entirely gone, but less and less is that a barrier to transplant, and it's also speeding up how quickly people can get to transplant because we're waiting less time to get perfect matches or unrelated donor matches. We can get by with a greater degree of mismatch and just take the patient in to transplant sooner in the course of their therapy, and I think there may be benefits for certain patients in that approach. So it really is changing how we're approaching the problem and making transplant an option for many more patients, and as you see from direct head-to-head comparison studies, we're also getting better outcomes on those trials. Fewer cases of graft versus host disease and fewer complications of transplant I think is a wonderful thing.

Dr. Karen Carlson (00:27:12):

So along that line, what is the timeframe between diagnosis, remission and then moving on to transplant? What's ideal from a timeline?

Dr. Alexander Perl (00:27:27):

I think in a newly diagnosed patient, the big question is risk stratification. So if a patient is adverse risk from diagnosis, you don't want to wait. As soon as the patient is stabilized and can go to transplant, that's the way that we would like to do it. They should receive induction therapy to stabilize their disease, but then get the transplant ready to go and just move towards transplant. In somebody who's judged to have more favorable disease, we're actually going to look to see how deep the quality of remission is because if the depth of remission as assessed by a measurable residual disease assay is inadequate, we may think about transplant even in somebody who's pretreatment baseline diagnostic genetics would suggest they're going to do well with chemotherapy. It just proves to us that they're getting an adequate treatment response and if they're not, this is a reasonable alternative.

(00:28:14):

And then there's everybody in between who have somewhere intermediate in terms of their genetic risk of their disease, and I think most centers are trying to get those patients an assessment to say is transplant better than chemotherapy? In many cases it may be, and then we try to move the patient to transplant expeditiously, usually within a cycle or two of chemotherapy to get them into remission, and then there can be some lead time to do the transplant. So it may take a total of two to four months from the time of diagnosis before a patient can go to transplant. And I think most centers to get to transplant on the quicker side of that rather than the longer side of that if a decision is ultimately made to do transplant.

(00:28:53):

And one other thing to just point out for transplant being the cure is increasingly we're looking at maintenance therapies after transplant too, and those may be important for subsets of patients. There's quite a bit of data looking at FLT3 inhibitors after transplant and for patients with FLT3 ITD mutation, it looks like that's important. There may be other patients who benefit, and there are ongoing studies looking at say oral hypomethylating agents or other drugs. Even venetoclax is being looked at post-transplant to see if that's going to lower relapse rates and improve survival as well.

Dr. Anand Patel (00:29:24):

One point that I wanted to highlight that the Dr. Perl brought up was transplant is not something that happens overnight in terms of once the decision or the discussion starts. Even with things moving in a very tight and fast manner, you're still looking at several weeks between when that decision is made and when the workup is ongoing and when a patient actually comes in for their transplant-related admission. So I think that's important to highlight because if transplant's being discussed, it's helpful to have a dedicated visit if possible, where really the ins and outs of transplant are discussed and that is what takes up the bulk of that visit, and then getting a good sense of what's needed. How will a potential donor be identified? Do I have siblings or children or other folks within my immediate family that need testing done to see if they could be a donor? Having all of that workup happening in parallel with receiving treatment for leukemia is what then allows for transplant to happen in a somewhat timely fashion.

Dr. Karen Carlson (00:30:33):

That is very helpful. I know we often have folks at our center wondering if they will be admitted for their treatment and then be discharged after their transplant is completed, and it's hard. It feels like a hurry up and wait when the stakes are really high, so I think that being very transparent about that and setting expectations up front is incredibly helpful, so thank you both for that information.

Dr. John Quigley (00:30:58):

And sorry, just to add in, Karen, because I think there was a specific question, somebody was asking what was the time period. And so to add to what others had said, usually we do an induction treatment and meanwhile, we've done HLA typing upfront and we're looking for donors. But if we feel that it's going to be more than four to six weeks after they've recovered from the induction therapy, then we'll go ahead and give another cycle just to make sure the patient doesn't potentially relapse.

Dr. Karen Carlson (00:31:31):

Absolutely. Do you ever transplant patients who are not in remission?

Dr. Alexander Perl (00:31:38):

We do. We do so with careful calculation, though. There's a weighing of would the patient be better served by additional therapy? If they hadn't had intensive therapy, something more intensive? If they've had intensive therapies, is it the best that we could see or should they see a second cycle of the same or something different? Is the donor ready? Are all other aspects of the transplant ready? All these weigh in, but there are data to say that if a transplant's the best ultimate therapy, that patients who are high-risk should receive it if all other things are equal. And a German group presented data on this topic at ASH and actually showed reasonably good outcomes from patients transplanted with active disease or at the time of a salvage regimen for some degree of refractoriness to initial chemotherapy.

(00:32:24):

It gets a little bit tricky when you're using a reduced-intensity transplant though, so for older patients or those with comorbidity, it's harder to advocate for that approach just because relapse rates in that setting are a lot higher, and so the benefits of transplant are a lot harder to weigh. And similarly, if anyone's had a relapse, to send someone into transplant with active disease is often associated with relapse soon after the transplant. And just is it really worth the trouble if the likelihood of relapse is really high? And that requires a very informed discussion with the patient, it's highly individualized. But

no, it's not impossible to do a transplant with active disease, but we really weigh that decision very carefully and the risks and benefits are a little different than a patient in remission.

Dr. Karen Carlson (00:33:08):

Understood. I guess I'll turn to some supportive questions for patients going through transplant. How do families and loved ones support them? And tied into that, are there ways that patients can recover, regain lost weight over the course of the transplant? Just general supportive care advice?

Dr. Anand Patel (00:33:33):

I'll say having a incredibly strong social network, whether that be friends, family or a combination of the two, is a must when thinking about transplant and someone going through the taxing experience of transplant. The other thing I'll add is there's actually a lot of considerations around optimization in terms of physical strength, dietary and otherwise that can happen before the transplant even takes place. So at our center at the University of Chicago, we actually have a program called the TOP Clinic, the Transplant Optimization Program. And really, any patient over the age of 60 is seen not just by a transplant doctor but a physical therapist, a dietician, a pharmacist who reviews the medications they're on, and several other physicians like an infectious disease doctor.

(00:34:27):

If they have a history of heart issues, maybe a cardiologist, et cetera, really with the goal of recognizing that whatever can be done to address things like diet and strength ahead of transplant is going to go a long, long way because when patients are ultimately admitted for a transplant, that can be oftentimes a three to four-week stay in the hospital. And even if you're doing all of the exercises you can in the hospital, just by virtue of being restricted in what you can do, some of that strength is going to be lost. And then really having that close follow up post-transplant where you are still plugged in with folks like a physical or an occupational therapist, a dietician, those things are so incredibly helpful to then help to regain what may have been lost over those several weeks during a transplant stay.

Dr. Karen Carlson (00:35:19):

Understood. Thank you. Another question on transplant. Someone asked essentially is there an age cutoff, an upper age limit for bone marrow transplant? Dr. Perl?

Dr. Alexander Perl (00:35:35):

I'm kind of chuckling because I think the challenge as we all get older is we want to say, "Oh, we're eligible for any therapy." And I'm not all that old, I'm in my fifties, but I think back to when I was in training, we wouldn't give an unrelated donor transplant to someone at my current age and now we have no difficulty doing that at all, but we might use a different preparative regimen. And as we look at patients getting older than 50 into their sixties, again, we might give a different preparative regimen in that setting even today. And as we get into the seventies, we might use a different immunosuppression approach, and as we get up to approaching 80, we're very careful about who we might recommend transplant at all for, not because there is a formal age cutoff, but just as we look at populations, it's harder to get away with the same kind of good transplant outcomes for patients as age increase overall.

(00:36:26):

But every patient is individual, so we don't like to say we have an age cutoff, we won't transplant anybody over the age of X because then somebody walks into the office who just finished the marathon last week and says, "I feel fine and ignore the date of birth on my chart," and they really are quite fit.

And so a thorough assessment of their medical fitness is critical at any age, and I think that's really, really important. That being said, it's pretty uncommon that we do standard transplants outside of a clinical trial in patients over the age of about 75 at my center. We do have a trial that is primarily enrolling patients who have significant comorbidity and are looking for a gentle as possible transplant because they may benefit, but we always have to look at the potential benefits of the transplant and the possibility it will extend your life versus the realistic risk of the transplant that it may shorten your life.

(00:37:21):

And there's real transplant-related morbidity that could be permanent after that kind of therapy, even if it does cure the underlying disease. And so we don't want to trade one disease for another and wind up with a worse outcome or wind up with no outcome because the patient could have lived longer without the transplant. So we're really, really careful about looking at patients who have any serious comorbidity, even when that comorbidity is otherwise successful aging. We don't have a formal cutoff that we would say, "We won't transplant her if you're a certain age," but I do think the number of transplants we do for people in their upper seventies, early eighties is relatively small and we virtually always will do that in a clinical trial. I don't think my center has transplanted anyone in the eighties to date. We've transplanted many patients in their upper seventies, but generally on trials.

Dr. Karen Carlson (00:38:06):

Got it. Thank you. I know there's a few more transplant questions, but I do want to make sure we hit some of the other topic areas, so if we can go back we will, but I'm going to switch to prognosis and survival rates. And we had one question specific to a 19-year-old person with a FLT3 mutation in their AML and a similar question for teenagers. What is the expected chance of full recovery and is their treatment standard everywhere? And so maybe I'll synthesize this to does age of the patient have an impact on survival from AML, and what is the impact of a FLT3 mutation on AML prognosis?

Dr. Alexander Perl (00:38:51):

Can I dive in on this one? This is kind of in my wheelhouse. So there's a few different kinds of FLT3 mutations. I just want to be careful because the most common FLT3 mutation is what's called a FLT3 ITD, and that's the one that historically has been the one that we worried about because it had a higher relapse rate and worse prognosis, and we would generally steer anybody with a FLT3 ITD at age 19 towards a transplant. And I think that that is still our preferred approach, but our outcomes are getting a lot better when we use these aggressive therapies. And Dr. Patel mentioned that FLT3 inhibitors added to frontline therapy such as midostaurin, which is standard, has led to better survival in that group.

(00:39:28):

And there were recently presented data with a newer drug that's being looked at by the FDA right now called quizartinib that may be even better than midostaurin and they've just not been directly compared. So hopefully that will be a drug that we hope will be approved and at our fingertips, and there's therapies for patients who have relapsed disease if they have FLT3 mutations, a drug called gilteritinib. So there's a bunch of new drugs that have improved the outcome of patients who have FLT3 mutations and those advances have happened at each stage of the disease, newly diagnosed post-transplant and also for relapsed disease.

(00:40:01):

There's no way to look at this and say, "What's the survival rate for an individual patient," because we have to see that you got appropriate therapy, responded well to it and that everything worked the way you want it to. But we're curing the majority of patients with newly diagnosed AML and FLT3 mutations

regardless of whether they are FLT3 ITD or FLT3 TKD mutations, and we're excited about that and that outcomes really are getting better over time for this subset of patients. But we're not at a point where we can say you can dial it down yet, you can give less than very aggressive therapy. If you have FLT3 ITD positive disease and you're a candidate for a transplant, I generally recommend that you get the transplant, and preferably with a FLT3 inhibitor prior to that transplant and after that transplant based on available data.

(00:40:45):

The other kind of FLT3 mutation is a FLT3 TKD mutation, and in some settings those patients have done extremely well and really may not need a transplant if they have a co-mutation in NPM12, and again, they're treated intensively and have an excellent response to therapy. So it's a hard question to answer without knowing more details, other than to say that we're happy that the outcomes for patients with FLT3 mutations, which used to be much worse, are actually doing much better. And the prognostic guidelines have downgraded FLT3 ITD from being a high-risk mutation to being intermediate risk, but that doesn't change my treatment recommendations. I still think those patients should be treated aggressively, intensively, including transplant in their management where possible.

Dr. Anand Patel (00:41:25):

I wanted to jump in and tackle this question through the lens of not FLT3 mutated AML, which I know is the specific prompt, but really acute lymphoblastic leukemia, or ALL, just given how we're thinking about age. And when thinking about ALL and transplant, broadly speaking, we do think of ALL largely as being a disease that can be cured with chemotherapy alone, assuming we achieve something called MRD negativity, with MRD standing for measurable residual disease. Meaning with our most sensitive techniques for identifying a spare leukemia cell that may be left behind, we are not able to detect anything. And we've seen excellent outcomes using regimens that our pediatric colleagues use for younger children with AML, so we've applied those regimens to what we call our adolescent young adult population, from the ages of 18 to about 40.

(00:42:25):

But when we get beyond that age of 40, we find that some of the medicines used in those pediatric regimens can be very hard on someone, so we may need to modify the doses or in this day and age, we actually have several targeted therapies for ALL that act upon certain cell surface markers that the ALL cells may have. So there's lots of work being done to figure out how to best sequence or combine those medicines. And I think to go back to Dr Perl's point, transplant or no transplant, when thinking about the spectrum of acute leukemias is almost never a one-size-fits-all decision or discussion, but at least from the lens of ALL, we more times than not tend to think of it as a disease that can be cured with chemotherapy alone. And then if there are situations where the disease is still detectable or the disease goes into a remission for some period of time and comes back, that's really when we think about how do we gain control again and then think about moving forward with a transplant.

Dr. Karen Carlson (00:43:32):

Thanks so much. I know we spent a lot of time talking about AML. I appreciate you bringing us back also to think a little bit about ALL. One last question about prognosis. If someone's AML has been in remission for five years, does that mean they're cured? Does it mean their life expectancy is what it would've been without a leukemia diagnosis?

Dr. John Quigley (00:44:02):

I can jump in here on that. Yes, I think the majority of leukemia physicians would say that if you're five years out, that you are cured of your disease. And related to what Dr. Patel was saying, with the improved outcomes in leukemias in children, that brought forward this idea of survivorship. And so survivorship has actually become a specialty now where survivorship clinics are held for patients who are cured of their disease, and the reason for that is because of the fact that there are side effects associated with chemotherapy that will present later. For example, potentially you can have heart problems, you can have psychological problems. You can have problems with your teeth, you can have bone osteoporosis, et cetera. So there's a whole defined group of symptoms and diseases that occur in patients who are cured of their disease that need to be monitored for, and so I would recommend that patients attend the survivorship clinic if it's available at their institution.

Dr. Karen Carlson (00:45:21):

I think that's very, very important advice. Thank you. Moving on to causes and risk factors, we had one question submitted that pertained to AML. Do patients that have multiple family members with AML have a higher chance of getting AML?

Dr. Alexander Perl (00:45:43):

This is a really important question because sometimes there's a family history and it turns out we can find a gene that predisposes a leukemia, and in some cases that can be important enough that we may actually counsel the unaffected family members to get either more frequent screening or in rare cases, to get therapy. So if there is a family history, it's worthwhile I think to talk to your physician about should you get that screening because it's getting easier and easier to do that in terms of the way that we can screen for this. It usually requires not a bone marrow biopsy or a blood test, but actually for the patient who is affected, the person who has leukemia, that they have a skin biopsy done and if there's a gene that's found meeting with a genetic counselor, sometimes even before the skin biopsy is done.

(00:46:35):

At our center we have somebody who specializes in this, who coordinates this, and they're very interested to meet with patients for the very reason that is presented here, "What's the risk to my family? But what I can say, and I often say to the flip side of this, which is someone wondering, "Where did I get this from? What about my kids? Am I going to pass this along?" Is in the absence of a strong family history, it's actually pretty uncommon that we find a gene that says this is why what happened to you is what happened to you. And I've found as I've sent people to, again my colleague who specializes in what's called inherited or germline predisposition to leukemia, is many of the patients that I thought would have a significant family history and that would lead to a gene, we don't find anything.

(00:47:18):

And does it mean that there's no family cause of this or no gene that's there? No, it's possible that we just can't identify it. But more likely than not, there are just chance reasons why people can develop leukemia and we never find a reason for that. And again, if there's not a strong family history, I think that's a reasonable way to say that you don't have to lose sleep over this saying, "Are my kids going to have to go through the same thing that I went through? Do I have to bring my whole family in for evaluation of this?" It's pretty uncommon.

Dr. John Quigley (00:47:45):

you go ahead, Dr. Patel.

Dr. Anand Patel (00:47:49):

Thank you, Dr. Quigley. I was just going to add one other subset of patients that we do think about hereditary or germline syndromes in are not so much patients who have a strong family history, but patients with a personal history of more than one cancer. So we have this entity of therapy-related leukemia, and that can be therapy-related AML or ALL, we're finding, so someone who received therapy and hopefully were cured of an initial malignancy or cancer, then potentially several years down the line have now developed a leukemia. So those patients are other patients where I think careful review of family history of cancer and then consideration for germline or hereditary testing should be considered.

Dr. John Quigley (00:48:32):

Could I just add in there that also patients who have a relative who has this solid tumor and less than 50 years of age is also important. And then obviously, the other important aspect is in terms of testing of siblings if there is a concern if these patients are in terms of donors for transplant is also very important.

Dr. Alexander Perl (00:48:55):

We just had a case, a clinic patient of mine who had the option of two siblings being donor or a unrelated donor who wasn't as well-matched as those siblings, and we found out the patient did have a germline predisposition as did both of his siblings and we chose the unrelated donor, so we're very glad we looked.

Dr. Karen Carlson (00:49:16):

Wow, thanks. That's wonderful information. I'm going to go from Dr. Patel's comment regarding therapy-related AML. I see we have a question that came up in our chat about how does having a therapy-related AML impact your choice of treatment?

Dr. Anand Patel (00:49:41):

I can start, and I'd love to have Dr. Perl and Dr. Quigley weigh in 'cause I think this is an area of much discussion. So right now, there is a therapy that carries an FDA approval specifically for this entity of therapy-related AML. It's called CPX-351, or Vyxeos is the trade name, and it's a formulation of two standard drugs that we use in intensive induction therapy for AML, which is cytarabine and daunorubicin. So there was a phase 3 study that was done now about five years ago comparing this novel formulation of these drugs, of Vyxeos, to standard 7 and 3 and there was found to be a survival benefit. That being said, Vyxeos is a medicine that does have toxicities, and particularly what was also seen was that when blood counts were knocked down from chemotherapy, they took on average about 10 to 14 days longer to recover, so patients potentially staying in the hospital longer and being at higher risk of infection.

(00:50:47):

With the effectiveness of azacitidine and venetoclax as a regimen for AML, there is a lot of discussion in our field right now about if this is a regimen that is as effective as something like Vyxeos or similar sorts of intensive regimens. And as of yet, this has not been something that's been looked at head-to-head, meaning patients being randomized to one of these two treatments. But what has been done, and actually quite a bit of work by Dr. Perl's group at Penn looking at this question, is they've looked at large cohorts of patients that have received either Vyxeos-based therapy or a hypomethylating agent in venetoclax-based therapy, and they've found what seemed to be fairly similar outcomes in the two

groups. And really, the big thing being if patients can achieve adequate disease control and go on to receive a transplant, those tend to be the patients that do best with a therapy-related AML.

Dr. Karen Carlson (00:51:50):

Terrific.

Dr. Alexander Perl (00:51:50):

I'll just follow that up saying we actually were surprised but kind of pleased to see that the outcomes when we looked retrospectively, meaning we looked back on prior data from both our center and also a nationwide database of electronically captured health information, something called Flatiron Database, showed actually really very similar outcomes from venetoclax-azacitidine and the more intensive CPX-351, Vyxeos therapy. They're really different therapies, and the challenge in interpreting this and saying, "Now we're ready to change our therapy," is these are not patients that we evaluated prospectively coming in the office and then randomized them. So actually, we're impressed enough to say that they're similar enough that we could reasonably choose one or the other, but the best way to say what's the best therapy is to actually do a study where you randomize patients and say, "We're not convinced that there's a big difference, but even if there's a small difference, we'd like to see what it is."

(00:52:45):

And we're participating in that study, which is currently ongoing. It's led by Amir Fathi from the Massachusetts General Hospital and it's a nationwide study, so a bunch of different centers are participating in it and we're one of them. So hopefully this will answer the question is intensive chemotherapy as good as ven-aza? Does ven-aza offer advantages? And I think for somebody with therapy-related disease, with the exception of people who have favorable genetics who do exist, transplant is often the best therapy once in remission and we think it may not matter that much how you get there, whether it's low intensity or higher intensity. As long as you receive that therapy, those patients really did the best in terms of long-term follow up.

Dr. Karen Carlson (00:53:25):

Oh, wonderful. I think we'll take one more question, and I'll take it from our participants who have typed in some questions as we're going. And this one is about ALL, which is a disease we haven't talked as much about this afternoon. Has inotuzumab or Blincyto been approved for frontline treatment for ALL, and is any approval in that instance similar for both children and for adults?

Dr. John Quigley (00:53:53):

I can answer that. I can tell you that at the moment, there are trials going through, so Alliance cooperative group trials. I'm sure we've all heard of the E1910 trial that was recently reported using blinatumomab as part of the regimen for ALL, which has markedly improved outcomes versus chemotherapy alone. In that trial there's a present Alliance trial, again a cooperative group trial, looking at use of inotuzumab again as part of the chemotherapy in frontline treatments. And I'm part of a group with Dr. Stock at University of Chicago. She leads this group that looks at new trials, and there are new trials coming out where people are looking at the idea of actually reducing the chemotherapy dramatically and just giving induction therapy and then using perhaps inotuzumab followed by blinatumomab followed by inotuzumab, trying to reduce the chemotherapy aspect of the regimen dramatically because of the effects of these great immunotherapy drugs.

Dr. Alexander Perl (00:55:19):

There's one other area that we're very excited about, which are the data that have come initially out of Europe and now are being expanded upon by the MD Anderson Group in patients with Philadelphia chromosome positive AALL, where tyrosine kinase inhibitors, BCR signaling inhibitors that work against the Philadelphia chromosome itself. The function of that gene translocation is that it activates an enzyme that can be inhibited by drugs, and that combined with immunotherapy has been the standard for years, which is using a tyrosine kinase inhibitor plus chemotherapy to go to an allo transplant and then using the bone marrow transplant's immune mechanisms to control disease along with the drug. And we're hopeful that we can use a drug like blinatumomab to maybe get rid of the need for an allo transplant or even get rid of the need for the chemotherapy you'd add to the tyrosine kinase inhibitor.

(00:56:09):

And so there's been some really exciting data presented from trials initially from Europe and then again from the MD Anderson group looking at dasatinib plus blinatumomab as frontline therapy, which showed really phenomenal results. And then more recently, ponatinib plus blinatumomab where the survival is just we've never seen anything this good, and we hope that this is a real finding that we can just bring to our patients. There's going to be a randomized comparison of these that's currently enrolling and hopefully will guide us as to what's the best therapy. So it's not yet standard to do that outside of a trial I would say, but I think a lot of people are hopeful that this establishes a new standard of care where we really don't need chemotherapy to anywhere near the degree or really at all in a subset of what used to be considered our highest risk patients and now maybe actually one of our more favorable risk patients through these advances in therapy. It's a really exciting time in ALL.

Dr. Anand Patel (00:57:02):

So to briefly summarize, right now ino is approved for adults with relapsed refractory B-cell ALL in terms of what the FDA approval is, and blinatumomab is approved in both children and adults with either relapsed refractory B-cell ALL or low levels of ALL that are detected by this MRD testing. But as Dr. Quigley and Dr. Pearl have very nicely outlined, the goal is really to see how these therapies can be incorporated into the initial treatment of ALL and see if their effectiveness can potentially reduce the need for transplantation or reduce the need for additional chemotherapy for patients with ALL.

Dr. John Quigley (00:57:49):

And sorry, Karen, just to jump in. I think it brings up a bigger issue, which is what Dr. Patel spoke about previously, this idea of minimal residual disease. And so the idea that we can actually detect very small amounts of leukemia cells in the body, in ALL certainly, really allows us to not be as concerned about transplant. So if we're not seeing any evidence of leukemia by these very sensitive testing, then we feel more confident about saying, "Let's just use chemotherapy and/or targeted therapies." And I think the issue now that we're all struggling with is how to apply this concept of minimal residual disease to AML to help us to chip away at this big group of patients with AML and try to figure out whether they need to go for transplant or not.

Dr. Karen Carlson (00:58:55):

Wonderful, thank you. Well, with that, thank you all so much. I'll turn the conclusion of this session over to Carrie.

Carrie Callas (00:59:03):

Yes. Thank you to our fabulous panelists, Dr. Patel, Dr. Perl and Dr. Quigley, for giving of your time today, and same with Dr. Carlson, who has been our moderator of both programs. All of our expert physicians today donated their time to be with us on this Sunday afternoon, so we greatly appreciate it. I also wanted to mention two upcoming programs in May that our audience might be interested in. One is about nutrition and leukemia. We have an expert oncology nutritionist who will be answering questions. Similar, she'll be presenting a little bit, but then also answering a lot of questions on nutrition. We also have another one in May coming up about managing graft-versus-host disease, which I know we talked a little bit about today as well.

(00:59:55):

[Closing remarks omitted].

Dr. John Quigley (01:00:36):

Thank you.

Dr. Alexander Perl (01:00:37):

Thank you so much.

Dr. Anand Patel (01:00:38):

Thanks, everyone. And thanks, Dr. Carlson, for her expert moderating.

Dr. Karen Carlson (01:00:43):

Thanks. Bye-bye.

Dr. John Quigley (01:00:44):

Thank you. Bye-bye.