LEUKEMIA & LYMPHOMA SOCIETY® is now

Blood Cancer United

## The Bloodline with Blood Cancer United Podcast

A podcast for patients and caregivers

# *Episode: 'Acute Lymphoblastic Leukemia (ALL): The New Tools Shaping Tomorrow'*

## Description:

With so many new advances in acute lymphoblastic leukemia (ALL), understanding today's treatment landscape can give patients a clearer, more hopeful outlook.

In this episode, we speak with Marlise Luskin, MD of the Dana-Farber Cancer Institute, about what adults should know when facing a diagnosis of acute lymphoblastic leukemia. Dr. Luskin helps listeners understand how ALL develops, how subtypes are identified, and why genetics play an important role in guiding treatment. She discusses current therapies including chemotherapy, targeted agents and immunotherapies including CAR T-cell therapy, as well as how care teams monitor progress and manage side effects. While ALL is a complex disease, patients and caregivers will hear clear explanations, practical information, and meaningful reasons to feel hopeful about the advances shaping ALL care today.

## Transcript:

**Elissa:** Welcome to *The Bloodline with Blood Cancer United*. I'm Elissa. Thank you so much for joining us on this episode.

Today, we are speaking with Dr. Marlise Luskin, a hematologist-oncologist at the Dana-Farber Cancer Institute in Boston, Massachusetts.

She also serves as the Associate Program Director of the Dana-Farber MGB Hematology/Oncology Fellowship, Director of The Foley Family Fellowship in Leukemia, and Education Director for the Division of Leukemia.

Dr. Luskin's areas of clinical and research interest include acute lymphoblastic leukemia, or ALL, blastic plasmacytoid dendritic cell neoplasm, or BPDCN, acute myeloid leukemia, chronic myeloid leukemia, and the care of young adults with leukemia. Welcome, Dr. Luskin.

**Marlise Luskin, MD:** Thank you so much for having me, Elissa. It's really great to be here.

**Elissa:** Well, thank you for being with us.

So, our episode today is on acute lymphoblastic leukemia, or ALL. Could you tell our listeners what that is?

**Dr. Luskin:** Yeah, well, thanks so much for inviting me to this program and letting me join your listeners talking about this disease called acute lymphoblastic leukemia or ALL. This is one of the diseases that I treat in my practice, and it's a disease that I really enjoy taking care of patients with this condition because of a lot of exciting new advancements over the ten years that I've been in practice.

So, acute lymphoblastic leukemia is a subtype of leukemia. Often when I meet patients, we spend some time talking at the beginning about the different types of leukemia because that word leukemia refers to a cancer in blood cells. But there are so many types of leukemias; and individuals may read about a leukemia or hear from a friend or family member about a leukemia and somebody else in their family or friend network, and it may be completely different.

So, an acute leukemia is a type of leukemia that tends to come on more quickly; and it's a cancer of immature cells or sometimes which we refer to as blasts. And there are two major subtypes of acute leukemia. One is called acute myeloid leukemia (AML), and one is called acute lymphoblastic leukemia. And they involve different parts of the blood system. Acute lymphoblastic leukemia is the most common acute leukemia in children, but it also affects adults; and it's an immature blood cell of the type of blood cells that normally then grows up to be a lymphocyte that circulates in the blood and it, inhabits lymph nodes. But when it becomes cancerous, there's an increased number of these immature lymphoblasts that then cause problems in the body.

**Elissa:** Okay, and we know there are different types of ALL, like B cell and T cell. What does that all mean?

**Dr. Luskin:** Yeah, it's a great question; and I heard one of my colleagues say to a patient recently that, you know, leukemia or a disease is like a fingerprint, that every individual case is unique. And I think that's important for patients as they get

information about their condition and they speak to their doctors because we have the ability now to really understand each individual patient's leukemia at a pretty detailed level which can really affect treatment decisions. But, we do group the types of leukemia in major categories; and the major categories that I often speak to patients about is whether that, not they have something called B-cell ALL or B-lymphoblastic leukemia or T-cell ALL, or T-cell acute lymphoblastic leukemia; and these are the two major subtypes of ALL that affect the two major types of normal lymphocytes, Blymphocytes or T lymphocytes.

**Elissa:** Okay.

**Dr. Luskin:** And the cancerous versions of those normal blood cells still kind of retain the characteristics of the normal blood cell counterpart.

Beyond that, the other major distinction that we also often think about is whether or not the patient has something called the Philadelphia chromosome, or Ph-positive ALL or Ph-negative ALL. And we make that big distinction because Ph-positive ALL now has a very specific approach to treatment based on treatments that have been developed specifically for that genetic subtype of ALL, whereas we tend to group other subtypes of ALL into this category of Ph-negative, though there are many subtypes within that. Most, but not all Ph-positive ALL is B-cell ALL. So often, I think about B and T and then within B, Ph-positive and Ph-negative.

Another thing that often can be confusing is that there are some forms of ALL where the cancer cells are not primarily inhabiting the bone marrow or the bloodstream. The bone marrow is inside the bones of the body, and that's where blood is made. In most patients with leukemia, the cancer cells, the blasts, fill up the bone marrow and, in some cases, circulate in the bloodstream. But in a subgroup of patients with ALL, those blasts really only inhabit other places, like lymph nodes or something called the mediastinum, the chest area, areas outside the bone marrow. And sometimes this can be referred to as lymphoblastic lymphoma.

**Elissa:** Oh.

**Dr. Luskin:** And that really refers to a different way that cancer cells are distributed in the body. But we approach the treatment often in the same way as ALL. So, ALL and LBL, as it's referred to, are two different versions of the same disease.

**Elissa:** Okay, now you mentioned Ph-positive and Ph-negative. Are there other gene mutations within ALL?

**Dr. Luskin:** Yeah. One of the advances over the last several years is increasing ability to characterize the genetic features of ALL, with Ph-positive but also with Ph-negative. And there is an ever-growing list of genetic subtypes, and to some degree, we are still trying to figure out how that information should affect treatment. But as we learn more, it is helping us tailor treatment to different genetic subtypes.

Historically, we have looked at something called chromosome abnormalities, and chromosomes are the bookshelves for the genetic material in all of our cells. And we've been able to look for big changes in the chromosomes – rearrangements or losses or additions of chromosomes. But now we have technology to look at even more detail level looking for gene mutations, something called gene fusions. Lots of technical terminology but basically for us to understand the the personality and what drives a person's leukemia.

There are a lot of ongoing studies trying to understand the behavior of different subtypes; and that's helping us understand is this type of leukemia going to be more responsive to chemotherapy or less responsive and allowing us to risk-adapt in certain ways. This is still an area of ongoing research, but I certainly believe that more knowledge is better; and as the years go by, we're learning more and more how to use the information that we're able to, to detect in a patient's case.

**Elissa:** That's really good to know for getting those targeted treatments.

**Dr. Luskin:** Exactly.

**Elissa:** Or, you mentioned it was kind of very unique to the person; and so having those targeted treatments available is so important.

**Dr. Luskin:** Yes. And so, sometimes there's targeted treatments; and sometimes there's not a targeted treatment but we know how to adjust nontargeted treatments,

in terms of monitoring and risk-adapting, meaning giving it more intensive or less intensive treatment based on how we predict the leukemia is going to behave.

**Elissa:** Yeah, absolutely. Now, what is the prognosis for adult ALL, and is that dependent on the gene mutation or their chromosomal abnormality or B-cell or T-cell?

**Dr. Luskin:** Yeah, that's a great question. So, historically, ALL research really was led by our pediatric colleagues; and we're so appreciative of all the advances they've made over the last 50 years really, beginning at places like Dana-Farber. Sidney Farber, the namesake of our institute, was the first physician who was able to start seeing treatment responses in children with ALL.

But we've come a long way, and as adult oncologists, we have historically started by adapting the treatment regimens that were so successful in children and have used those regimens in adults. Fortunately, our pediatric colleagues are, are curing the majorityof children with ALL. We're so happy, and we've celebrated their successes; and one of our goals has been to bring that success to our adult patients – ranging from younger adults to adults in their later years. There's such a range in age groups and medical status in our patients.

But overall, historically, the outcomes for adults have not been as good as in children. The things that can help us predict how well a patient might do, we do know age has

an impact that can, number one, affect the ability for an individual to get intensive treatment programs and get those effective treatments.

We also know that in older patients, more likely to have a genetic subtype that is more treatment resistant; and so that goes to your question about genetic risk and learning more and more and be able to characterize more of the cases that we see. And we do know that some subtypes are more difficult to treat than others. So, age, genetic subtype.

And then, some other features, we do know that how high a white blood cell count is at diagnosis, which is a very simple test. They're the first lab test that is often checked when a patient comes to the clinic or the hospital. That can certainly impact via a marker of how aggressive the disease is.

And then the other thing that we use is how well is a patient doing? We have the ability now to detect leukemia cells at very low amounts in the body, and that's a test called measurable residual disease, or minimal residual disease, or MRD. And we have increasingly sophisticated tests to measure any little bits of leukemia that remain after initial treatment. And we know that how fast a person is able to clear their MRD is a marker of how well that disease is likely to stay away.

So, when I look at a patient and try to figure out how challenging is this case going to be, what are the chances I'm going to be able to cure it, which is always my goal

certainly when I first meet a patient. I think about age, ability to receive treatment, and then I look at the characteristics of the disease, the white count, the genetics, and then how well a disease responds.

**Elissa:** So, you'd say then between the pediatric and adult patients with the difference in prognosis, so is the disease itself presenting differently? In those adults, you talked a little bit about maybe different subtypes or treatment-resistant subtypes.

**Dr. Luskin:** Yeah. In a lot of ways, the clinical presentation for a younger adult and an older adult are similar. There's a large range of how we meet patients. I've even seen patients who get picked up by accident with routine bloodwork; and they notice their blood counts are abnormal. A common scenario is relatively generalized symptoms – a cold, shortness of breath, fatigue, sweats. Often patients think they have the flu or they have a more common illness that then gets evaluated when it doesn't resolve or is more severe than usual.

And then, occasionally, I'll meet patients who are very, very sick when they come to the hospital due to the aggressive nature of their condition. So, it's a large range and when I meet a patient, I sometimes need to hospitalize them right away because of how they're feeling or the impact of the disease on their organs or their medical stability. Though, I tell patients that a hospitalization isn't necessarily an indication that things aren't going to go well. It's a way to make sure that we stabilize them and

protect them from any complications and get all the answers we need as quickly as possible to come up with the very best treatment regimen for them.

**Elissa:** That's good to know. Now, what are the current treatments for ALL?

**Dr. Luskin:** Yeah. Well, that's a great question. I'm so glad you asked it because I get to list more things than I used to when I started in this career a number of years ago.

The first thing I will say is that what I'll term as conventional chemotherapy still plays a role in treating adults with ALL. So, when I refer to conventional chemotherapy, I'm talking about different chemotherapy drugs that have been used in combination. Really, developed by our pediatric colleagues that I was referencing.

And these include a number of different chemotherapy drugs. Steroids or corticosteroids play a major role. Something called vincristine, something called anthracycline are core drugs. But then we integrate lots of different types of drugs over the course of the leukemia treatment.

And our pediatric colleagues have learned over the years how to combine these drugs together so that the toxicities are not too difficult and to try and attack the leukemia with different drugs that may work in different ways. And they really, over serial collaborative protocols over 50 years, have really figured how to get patients into remission and then make those remissions stick. Get rid of any residual disease in the body in something called consolidation, followed by something called maintenance,

low-dose chemotherapy. And we know these prolonged combinations of conventional chemotherapy can cure many children and can cure some adults.

Another unique drug that is a real core component of pediatric regimens and used in our regimens that we use in young adults, is a drug called asparaginase, which is a really interesting drug. It's really an enzyme. The cells in our body need an amino acid called asparagine to help synthesize proteins and build cells and keep the metabolic machinery of the body going.

Normal cells can extract asparagine from the bloodstream or synthesize it on its own. But ALL cells need to steal that amino acid from the bloodstream. And so, when we give an enzyme that depletes that, we give an enzyme called asparaginase to deplete the amount of asparagine in the bloodstream. We can essentially starve the cancer cells.

**Elissa:** Oh.

**Dr. Luskin:** So, this is a real core component of pediatric regimens; and it was a major advance and helped increase the cure rate. But it has some particular side effects that can be more difficult for older adults to tolerate. Because it affects a number of other sort of normal processes in the body, older adults don't tolerate the drug as well in terms of what we call metabolic side effects. It can cause stress in the liver, the pancreas, the blood clotting system.

So, this drug was avoided for many years in adults and not used very heavily. But colleagues of mine, Wendy Stock and other colleagues about 20, 25 years ago, recognized that young adults who were treated with pediatric-type regimens with asparaginase did a lot better. And so, that really led an effort to more routinely treat what we call AYAs, or adolescents and young adults, who are in good shape up to the age of 40 and even 50 to use the asparaginase-heavy pediatric regimens in these younger adult patients. Her efforts to demonstrate that this was possible in perspective protocols was a major step in improving outcomes for our younger patients.

**Elissa:** So, that's that pediatric versus adult protocol where you wouldn't have that?

**Dr. Luskin:** Yes, so exactly. So, the pediatric-inspired regimens or pediatric protocols, unfortunately, we as doctors have to give multiple names to the same thing. And I'm sorry about that, but that's something that we, for our patient in the appropriate age group, will talk about whether or not we think they're a good candidate for a pediatric-inspired regimen or a pediatric regimen.

So, conventional chemotherapy is still a major component of treatment; and as you sort of alluded to more traditional adult regimens, use the same chemotherapy building blocks but use no asparaginase or less asparaginase and tend to decrease the doses of the chemotherapies or age-adjusted chemotherapy. Most regimens will have

guidance for how to adjust the doses of the medication based on somebody's age group.

The exciting thing that we've really been focused on the last five, ten years is bringing novel agents. You know, that's the kind of term we use for it, just because of new agents into the initial treatment of ALL for actually patients of all ages.

About ten years ago or so, we started to see approvals of new agents, particularly for B-ALL for leukemia that didn't respond to conventional chemotherapy. And so, the two drugs that were approved were a drug called blinatumomab or blina, which is what we call a bispecific antibody where one end of the antibody targets a marker called CD19, which is on the surface of B cells. And the other end targets a marker called CD3. That's on the surface of T cells, an immune cell. And that drug, basically, tries to get a patient's own T-cells to stop falling asleep at the wheel and come and attack the ALL cells.

So, this drug was approved for relapsed leukemia; and once that was approved, fortunately, research didn't stop. And the drug has continued to be studied and now integrated into the full spectrum of leukemia treatment. The idea being, if this drug works for leukemia that didn't respond to chemotherapy or came back after chemotherapy, why not use it out of the gate? Why not try to get it right the first time?

So, what we saw was that this drug worked for relapsed disease better than chemotherapy. And then we tried it in people who had little bits of disease left, meaning they responded but still had some of that we call MRD and low levels of disease. And it worked even better.

**Elissa:** Oh.

**Dr. Luskin:** The response rates are higher if there was less leukemia around; and so, the response rate went from about 40% for relapsed disease to about 75% for patients with just little bits of disease.

And then, we just naturally brought that forward and said, well, why don't we just bring it into combine it with chemotherapy in frontline protocols in frontline treatment and say, we'll give chemotherapy, but we'll take breaks periodically and give some cycles of this blinatumomab.

And that's really been the most exciting advance over the last few years that we have now randomized studies in both adults and more recently in children showing that integrating a couple of cycles of blinatumomab into the chemotherapy regimens improves outcomes, even in patients who are doing well with chemotherapy. Even patients who have responded, and you think they're doing well, we kind of ensure that they're going to continue to do well and increase the number of patients who stay in those remissions.

So, for B-ALL, blina is now a component of frontline therapy for all patients who express that CD19, which is not all, but the vast majority of patients with B-ALL, 90%+. And so that's really exciting for us.

**Elissa:** Now, is that replacing stem cell transplant?

**Dr. Luskin:** So, that's a great question; and these are questions that we're trying to answer. So, for all of our patients, were giving sort of age-appropriate chemotherapy, we're bringing in blinatumomab routinely, and we're seeing that more patients are being cured with their chemotherapy plus blinatumomab regimens. And so that, naturally, brings the question, who needs something called an allogeneic stem cell transplant or bone marrow transplant, which has, historically, been the most aggressive way to try to cure acute leukemia, including ALL. And who should get that transplant is something that we are continuing to try to refine. And this is certainly something that patients should have an individualized conversation with their physician.

**Elissa:** Yes.

**Dr. Luskin:** We still think it's a valuable treatment tool, but we want to offer it to patients who we think will benefit, for whom we think it will increase their chance of cure, and have patients that are going to do well without it not have to go through it.

We want to use it when we need to, but there are risks associated with transplant; and so, if fewer patients need it, that's something that we are happy for.

So, I would say that transplant is still recommended for some patients who have some of those high-risk features. There are certain genetic subtypes that, even with the blinatumomab, we're still worried that the disease will come back. And for patients who don't have that early response in terms of MRD, we'll have that conversation. So, it's something that we're still recommending, but we're being more selective about it.

And then what I would say is for patients who do still need that transplant, blina allows patients to get into a really good remission before the transplant, which increases the chance that transplant is going to be successful. And given that blinatumomab also has relatively few side effects, it doesn't have all the sort of same side effects of conventional chemotherapy. It can help patients get into a really good remission and allow them to be in really good shape when they enter that transplant to give them the best chance of having successful, effective transplant and set them up for having fewer complications.

So, blina, I believe, is allowing some patients to be able to get treated without transplant. And for those that do need the transplant, I think it's improving the chance of getting to that transplant and doing well with the transplant.

**Elissa:** That's good.

**Dr. Luskin:** There are other treatments that have been approved for disease that has come back or hasn't responded to those frontline-approved drugs, conventional chemotherapy and blina. Inotuzumab ozogamicin, or ino, as I say for short, is another antibody therapy that targets another marker on the surface of B cells, which is called CD22. That antibody only targets one marker, but the end of that antibody has a little bit of chemotherapy at the end of it. I call it sort of a smart dart.

**Elissa:** Oh!

**Dr. Luskin:** And this drug is effective for relapsed ALL but has this marker, which again, is not all but the majority of B-ALL. And the nice thing about this drug, in comparison to blina, which I mentioned really works best when there's just a little bit of disease in frontline treatment, ino seems to, the data shows us that it's effective for patients with a lot of disease as well as a little disease, which can be useful in those difficult situations where the leukemia does come back, and there's a lot of it around. It's a way where we have a good chance of getting patients back into a remission. So, that's an important tool in our tool kit for a disease that's come back.

This drug is being studied in frontline treatment, just like the blinatumomab. It's been studied in a number of settings; but in the area that we're particularly interested in developing this drug and for which there have been a number of trials around the world, it's been for older adults or more mature adults, if you will, who have the most difficulty with the chemotherapy. And they need a way to get into remission safely

without having to be exposed to a lot of chemotherapies. There have been a number of trials primarily in Europe and the U.S. using inotuzumab as an induction instead of conventional chemotherapy and then following it with either dose-reduced chemotherapy or the blinatumomab that's approved.

So, this is something that is now, what we've seen the last couple years, a lot of initial publications of the strategy; and it's a treatment approach that is now recommended in our guidelines for patients who are not good candidates for chemotherapy.

There's also ongoing trials in younger patients, pediatrics and young adults using inotuzumab in the frontline setting.

We're still waiting for the results of these studies to be fully available; and so, I would say it's not standard in that setting yet but something that we will be waiting for, to understand whether or not this is something that should be routinely used in those settings going forward.

**Elissa:** So, what about CAR T-cell therapy because I know that it was developed early on and used in pediatric ALL patients? Is it used in adult ALL patients?

**Dr. Luskin:** Yeah, that's another place where our pediatric colleagues led the way.

**Elissa:** Yes.

**Dr. Luskin:** And the first approval for CAR T in ALL was a product that was only approved for children and young adults up into the mid-20s. But fortunately, the last couple years, we've seen approvals for two CAR T products for adult ALL, regardless of age.

**Elissa:** Wonderful.

**Dr. Luskin:** And so, that is really a major improvement. And one is called brexucabtagene autoleucel or brexu-cel, and one is called obecabtagene autoleucel or obe-cel.

And this has really been another major advance for our patients. These treatments are approved for CD19-positive relapsed ALL. We're trying to have fewer patients relapse, as I've been emphasizing. But there are situations where that does happen. And this can be a valuable option for our patients. Sometimes, we'll use this as a way to get somebody into a good remission on their way to transplant in their second remission, and we're starting to learn more that a subset of patients can have really durable remissions from these treatments and may or may not need a transplant afterwards. And certainly, for a patient who might not be eligible for a transplant, that's, obviously, extremely important.

We're still learning who those patients are that are going to have the most long-lived response and we can safely recommend avoiding a transplant. And so, that's also a

very individualized decision that a patient should speak to their physician with. Patients who are younger who have a good transplant donor who are good candidates for transplant, we often will still recommend that; but it's an area of active research; and we're hoping to see CAR T be increasingly successful and, again, may be another way that we're able to reduce the number of patients who need transplants or do well when they're not eligible for a transplant.

**Elissa:** That's great.

**Dr. Luskin:** That treatment though is only approved for patients who have disease that's come back after a prior treatment. But again, there's a lot of interest in moving these more sophisticated treatments into earlier lines of therapy; and there are some very innovative trials starting with older patients who are, again, not good candidates for chemo and transplant using this as a consolidation strategy. So, if that's of interest to a patient, they really should be looking and asking about whether there's any clinical trials in their region to participate in an approach like that.

**Elissa:** Good to know. We will make sure to have information on our Clinical Trial Support Center (CTSC), so they can go and look for those trials. Now, you mentioned a lot of treatments for B-cell ALL. Are those treatments still good with T-cell ALL or are there different treatments for them?

**Dr. Luskin:** Yeah, no, it's a really important point. And we talked about ALL as one disease; but there are many different disease subtypes within ALL. And T-ALL, when we think about chemotherapy treatments and historical treatments developed in the pediatric setting has been the same for B- and T-cell ALL.

But the approach is now differing more because all of the novel agents that I just mentioned are developed based on their ability to target markers that are only on the surface of B cells. And so those particular novel agents, blinatumomab, inotuzumab, CD19 CAR are not applicable or not effective or helpful for patients with T-ALL, unfortunately.

We have had slower progress for T-ALL, and so, there are no other sort of approved novel agents for frontline treatment. There is ongoing research trying to address this subtype of ALL with an unmet need; and I think it's important to recognize that this is an area that does need attention in the research environment and clinical trials.

One approach that I've been involved in a study in the role of a drug called venetoclax, or Venclexta®, which is a pill that helps target a particular target called BCL2 and helps make cancer cells more vulnerable to dying in the context of chemo.

This is a drug approved for AML (acute myeloid leukemia), a different type of leukemia. We're studying it in ALL in older adults who can't tolerate high doses of chemotherapy to allow us to give them less chemo but still maintain potency. And

we're studying that in both B- and T-ALL, but I think it's a particularly important option to have for T-ALL who don't have access to the other options like blina and ino and CD19 CAR T.

There are a lot of smart people working in the research labs and we're hoping to see more innovation come down the pike or come online.

CAR T has been much more successful in B-ALL and also other types of B-cell lymphoma, been more difficult to apply to T-cell ALL. But we're recently seeing some early reports of clinical trials using really advanced technology to develop CAR T for T-ALL. And while we're not really there yet for routine practice, it's really only being done in the context of clinical trials, we're hoping to see progress for that in the future.

**Elissa:** That is so exciting, and we'll be ready to report on it when it is ready to go. Now, you brought up AML treatment, and I want to ask about something that I've heard recently is menin inhibitors. And I've heard that there might be a possibility for use with ALL with the KMT2A mutation. Could you talk about what that is and the possibilities for those patients?

**Dr. Luskin:** Yeah. So, KMT2A rearranged leukemia this is one of those genetic subtypes that we've been kind of mentioning generally. KMT2A-rearranged leukemia is a specific genetic subtype of ALL that's actually common in infant leukemia but then is very rare in children, but then becomes more prevalent in adults. A significant

minority of adults have it, so, we see it commonly. And this can be traditionally one of the more aggressive leukemia subtypes that I've sort of been referring to. Can be treated with chemotherapy but is more likely to not respond to chemotherapy or come back after an initial response to chemotherapy.

And most of the time these are B-cell ALLs, meaning that most of the time a KMT2A-rearranged leukemia is B-ALL. But they often don't express those markers, 19 and 22, at high levels or they're sneaky. The cancer cells can drop those markers as a way of getting around those targeted agents.

So, just like T-ALL, a high-risk subtype; and the novel agents that we have that are so effective for other subtypes of B-ALL cannot work as well. But fortunately, this drug that you mentioned, something called a menin inhibitor, targets one of the proteins that sort of is dysregulated in this particular genetic subtype. It's a complex molecular biology that, some of my colleagues really figured out. And that has been followed by the development of pills or menin inhibitors for patients with KMT2A-rearranged leukemia. And this abnormality can be seen in AML as well as ALL. And so, the approval for the first menin inhibitor applied regardless of whether it's AML or ALL.

This is a really important step forward. It's by no means solved the problem. The response rates are not as high as we like and not for as long as we like. But it is definitely offering us an option to help get patients back in remission and move to a more definitive treatment, like a transplant.

**Elissa:** Very exciting.

**Dr. Luskin:** So, thank you for bringing that up. The more tools we have the better and, after drug's been approved, then we study how to use them even better. You know, how do we combine them? How do we bring them into the right treatment setting? Should we be using menin inhibitors upfront, just like we're using blina upfront? And so, I think we're going to see more reported on that over the coming years.

**Elissa:** Okay. Now, let's talk about side effects because there's side effects that come with these various treatments. Could you talk about the common ones and if they can be managed.

**Dr. Luskin:** Yeah. One of the challenging parts about that question is because we have lots of different treatments for ALL, the side effects any particular person may be experiencing will really depend on the treatment program prescribed. And so, again, it's really important for patients to ask questions about what to expect with their treatment.

Sometimes, I think it's challenging because when a patient gets a diagnosis and a treatment recommendation, the doctor may outline what they're expecting for the next year or two. And that can involve many different phases with different treatment regimens, and there's just no way you can really absorb all of that all at once. And so, I often tell my patients, I'm going to go through side effects a little bit in general; but

we're going to break it down. So, as we get to the next month or the next module of treatment, we're going to talk about that module. And then we get to the next module, we'll talk about this module.

And we break it down, and we really focus on the side effects that they're experiencing currently or what they're most likely to experience in the near future, so they can prepare going forward because it's important to know what to recognize and that way we can be proactive about managing and minimizing those side effects. I think that's really important, Elissa.

There are a lot of things we can do proactively. And then if we hear from patients early on with a treatment problem, getting on top of those side effects early can be very helpful.

There is a lot that we can do. I think it's important to recognize that there's no way to eliminate side effects; but that knowledge, it helps the physician, the nurses, the nurse practitioners, the physician assistant, the pharmacists work with each individual to develop a supportive care plan that's tailored to them.

The side effects of the conventional chemotherapy are different than the side effects of the new treatments. And so, really understanding and learning about each of those, I always tell patients, "They can't take their whole semester of school in one day. To do one lesson plan at a time." And that's something that we really try to work; and I sort

of say, “Here’s a roadmap of what we’re going to experience,” and then we do many lessons along the way.

**Elissa:** Yeah, that is good. And it’s a good reminder for patients to be communicating with their treatment team because you do have solutions for them to try to either prevent it or to manage it. I’m an AML survivor, and I remember when I was just getting started with treatment. My doctor said to me, “Please, tell us if there’s anything going on. If you’re nauseous, if you’re having any of these other symptoms, we want to know about it so that we can try to make it better and make this experience better for you” because I think that people assume that it’s just going to be absolutely miserable.

**Dr. Luskin:** Right.

**Elissa:** And that is not necessarily the case if you’re communicating with your team and you’re getting managed.

**Dr. Luskin:** Absolutely. I usually tell people, “I’m not sure I can make you feel perfect, but I can certainly make you feel better.” Even if it’s something that you’re not sure if it’s a problem, I say, any individual patient it’s the first time they’re going through it. So, they don’t know what’s normal or abnormal, and I say, “Well, there’s nothing normal about this experience, but I can tell you what’s normally abnormal,” you know, or help you say, “Okay, that’s expected, don’t worry about that.” Or , “Oh, we should see you tomorrow.”

So, communication is really helpful; and I always tell the patient if they wake up in that morning and they have a question, don't wait till 4 PM. We'd rather call about something the morning and find out that it's nothing that needs to be addressed than end of the day where it's much harder to troubleshoot. Earlier in the day we can get patients into the clinic or other ways to try to stay ahead of the problem before there's an emergency at night.

**Elissa:** Exactly. And there's no stupid questions. There's nothing bad to say. Just bring it up and, hopefully, it's something that can be managed right away.

**Dr. Luskin:** And use your whole care team. Many practices have care teams. They have the physician. They have the nurse practitioner. They have the nurses. They have the pharmacist. They all have something to add. We try to do our best, but I'll tell you, my nurses think of things all the time that I didn't think of or they pick up on things; and I certainly couldn't take as good a care of my patients without their help. And, you know, it takes a team.

And patients. They bring their team with them; and every patient is different, whether it's family or friends or whoever they want to be involved on their behalf. There's no script. It doesn't have to be a specific person. It can be anybody that they trust and that they want to have asking questions on their behalf. And just make it clear to your doctor who's allowed to all in and ask questions on your behalf.

**Elissa:** Yes, absolutely. That is a very important.

Now, in your discussion of a lot of the current treatments, you talked a little bit about the future of ALL treatments and where we're going with that. Is there anything else, any other emerging therapies or clinical trials that you were particularly excited about?

**Dr. Luskin:** Well, I think I sort of touched on some of them; but I think what we're going to see going forward is, conventional chemotherapy still has an important role, particularly for our younger patients. But I think there's going to be increasingly less of a reliance on that or an ability to decrease the intensity of that conventional chemotherapy as we combine in the novel agents. I give a talk where I say, for our younger patients, let's get the best of both worlds.

**Elissa:** Yeah.

**Dr. Luskin:** Let's not give up on these decades of progress where we're now curing, 90%+ of children. We don't want to throw out all that knowledge. You need to make sure that you continue to do proven, effective treatments. But let's incrementally see if we can swap out some of the drugs that have a little bit more side effects and the long-term late effects and bring in these novel agents.

So, I think we're going to see that the treatments we have, we're going to learn how to deploy them better and for each age group and figure out what's the right amount of

chemo for each age group, and our most mature patients, maybe, chemotherapy-free regimens. And our younger patients, even though they can tolerate chemotherapy, maybe we can decrease that. So, I think we're going to see that.

And then, there are other drugs in the pipeline in Phase 1 trials of better blinas and better antibody therapies that may be more effective and have even an improved side effect profile from what we want.

**Elissa:** Yeah.

**Dr. Luskin:** There are people on the labs really understanding biology, including T-ALL; and I'm optimistic that we're going to see more drugs available for those disease subtypes as well. So, we've made a lot of progress. Our stats are better; and that means individual patients who contribute to those stats are doing better. And there are more patients who are living longer and being cured. But it's still not everybody, and that's important to recognize that there may be listeners here who are having a difficult time or the disease isn't responding; and that can be hard to really understand when you're hearing a lot of the overall positivity of this discussion. And so, we need to do better for those patients, figure out how to tailor treatment for them.

**Elissa:** Yes, definitely still more work to do, but it's very exciting to see how far we've come in just the, past 10, 15 years. So, that's wonderful.

Now our final question today, on our patient podcast home page, we have a quote that says, "After diagnosis comes hope." What would you say to patients and their loved ones to give them hope after a diagnosis of ALL?

**Dr. Luskin:** I would say whenever somebody hears that word "leukemia" or "acute leukemia," it's such an overwhelming diagnosis; and the immediate response is often shock and fear. But I would say that there's a lot of hope for anybody who walks in my door. Often when I meet them, I don't even have all the information, but I say, "Even without knowing the information, I know that I'm going to have effective treatment for you. I'm going to have hope that I'll get you into remission, and that I'll keep that remission around for a long time. And that we have lots of different options to make you feel better and give you more time in this life."

**Elissa:** I love that. Well, thank you so much, Dr. Luskin, for joining us today and for this wonderful discussion all about ALL and so many tools in the toolbox for patients and we hope this does give a lot of hope to patients for the future and those currently in treatment. And so, thank you so very much. We really appreciate you.

**Dr. Luskin:** Oh, it's really been a pleasure to be here; and I hope that this has been helpful for your audience.

**Elissa:** And thank you to everyone listening today. *The Bloodline with Blood Cancer United* is one part of our mission to improve the quality of lives of patients and their families.

Did you know that you can get more involved with *The Bloodline* podcast? Be sure to check out Subscriber Lounge where you can gain access to exclusive content, discuss episodes with other listeners, make suggestions for future topics, or share your story to potentially be featured as a future guest. You will also receive an email notification for each new episode. Join for free today at TheBloodline.org/SubscriberLounge.

In addition to the Lounge, we could use your feedback to help us continue to provide engaging content for all people affected by cancer. We would like to ask you to complete a brief survey that can be found in the show notes or at TheBloodline.org. This is your opportunity to provide feedback and suggested topics that will help so many people.

We would also like to know about you and how we can serve you better. The survey is completely anonymous, and no identifying information will be taken. However, if you would like to contact Blood Cancer United staff, please email, TheBloodline@bloodcancerunited.org. We hope this podcast helped you today. Stay tuned for more information on the resources that Blood Cancer United has for you or your loved ones who have been affected by cancer.

LEUKEMIA & LYMPHOMA SOCIETY® is now

Blood Cancer United

Have you or a loved one been affected by a blood cancer? Blood Cancer United has many resources available to you – financial support, peer-to-peer connection, nutritional support, and more. We encourage patients and caregivers to contact our Information Specialists at 1-800-955-4572 or go to BloodCancerUnited.org/PatientSupport. You can find more information on acute lymphoblastic leukemia at BloodCancerUnited.org/Leukemia. These links and more will be found in the show notes or at TheBloodline.org.

Thank you again for listening. Be sure to subscribe to *The Bloodline* so you don't miss an episode. We look forward to having you join us next time.