LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Understanding AML: The Challenges, The Progress, The Hope'

Description:

Acute myeloid leukemia (AML) is one of the most aggressive blood cancers—but science is making real progress. In this episode, Dr. Eytan Stein of Memorial Sloan Kettering breaks down what makes AML so challenging to treat, how it's classified, and the latest therapies changing the outlook for patients. From combination therapies and menin inhibitors to future research on CAR T-cell therapy and bispecifics, this is a hopeful, expert-led look at the future of AML treatment.

Transcript:

Elissa: Welcome to *The Bloodline with LLS*. I'm Elissa.

Lizette: And I'm Lizette. Thank you so much for joining us on this episode.

Elissa: Today, we will be speaking with Dr. Eytan Stein, the Chief of the Leukemia Service and Director of the Program for Drug Development in Leukemia at Memorial Sloan Kettering Cancer Center in New York City. Dr. Stein's research is focused on development of new treatments for myeloid malignancies, like acute myeloid leukemia, or AML. He played a key role in testing and getting FDA approval for two new IDH inhibitors and is a lead investigator in the Beat AML Master Clinical Trial. At Memorial Sloan Kettering, he leads early phase clinical trials to find better treatments, including research on why some cancers resist certain drugs and how new therapies like menin inhibitors might help patients with specific types of leukemia. Welcome, Dr. Stein.

Eytan Stein, MD: Hi. How are you?

Elissa: Good, good. Thanks for being here with us today.

So, our episode today is on acute myeloid leukemia, or AML. Could you please tell our listeners what that is?

Dr. Stein: Yeah, happy to do it. Acute myeloid leukemia is a disease or a cancer of the white blood cells. It's a cancer where you get too many immature white blood cells in your bone marrow, and those immature white blood cells crowd out your normal cells from being able to grow and do what they're supposed to do. So, it is not uncommon for patients with acute myeloid leukemia to have low platelets and also to be anemic, and that's because those immature white blood cells are just keeping the bone marrow from functioning normally.

Lizette: And what might bring someone to the doctor? Are there any common signs or symptoms of AML?

Dr. Stein: Yeah. The signs and symptoms of AML typically relate to the low blood counts that I just mentioned a second ago. So, I think there are sort of two ways that people come to my attention. The first way is a person might become very anemic. And when you become very anemic, they'll start feeling tired, feeling short of breath when they're doing activities that they were normally able to do without any issue at all. I've had young patients who used to run marathons; and then they try to run, and they're feeling really tired and don't understand why. So, they go to the doctor. They have a blood count done, and that shows that they're anemic.

Another way that people sometimes come to my attention is that they'll have some unusual bruising or bleeding; and I'm not talking about like little bruises where you bump yourself. I'm talking about blood in your stool in a way that's really abnormal or big bruises on your body when you didn't injure yourself in any way. So, that's another way that people end up going to a doctor, getting a complete blood count, and then they get sent to me.

And the final way, which is less common but happens is that, especially an older patient might be going to their doctor for a routine physical or because they're having

some other medical issue dealt with like high blood pressure or high cholesterol, they'll get a complete blood count. The primary care physician will notice that there's something abnormal about their bloodwork, and then they'll send them off to a hematologist like me.

Elissa: Okay. So, we know that there are gene mutations or chromosomal abnormalities associated with AML. Could you tell us more about those mutations and any other factors and how they are used to classify AML?

Dr. Stein: Yeah, so that's and important topic. So, I think the thing to remember is what I told you a couple of minutes ago, that AML fundamentally is a cancer where patients get too many immature white blood cells in their bone marrow. But how you get to that point biologically of having too many white blood cells in your bone marrow can happen in a variety of different ways.

And what I mean by that, is that there are different gene mutations and chromosome abnormalities that can develop in the bone marrow that can lead to this cancer. So, it's not all one thing that goes wrong and then you have this cancer. There are a variety of different gene mutations or different chromosome abnormalities that can lead to the same disease, which is acute myeloid leukemia.

Something that's important to note, and I get asked all the time by my patients, is whether these gene mutations, which I'm going to describe in a second, and chromosome abnormalities, whether they're inherited.

And the answer is that in the vast majority of cases, they are not. These are mutations that develop just as a consequence of the cell division that goes on in all of our bodies, and there is some cell that just went wrong.

Elissa: So, not a fault of their own?

Dr. Stein: Exactly. Nothing that a patient did can make this happen or keep it from happening. They haven't done anything wrong.

There is a small number of patients, maybe 3 to 5% of patients, who will have an inherited factor that can lead to the development of acute myeloid leukemia. Typically, it's not that difficult to figure that out because you'll meet a patient who has a parent or a grandparent or a brother or a sister who also had a disease like acute myeloid leukemia; and that sort of tips you off.

But with these gene mutations and chromosomal abnormalities, and every patient with acute myeloid leukemia has some gene mutation or chromosome abnormality that led to the disease. What we do is we look at those gene mutations; and then we stratify patients and say, "Well, this set of gene mutations put you into a group of patients where this particular treatment is likely to be successful while this group of gene mutations might put you into a different group of patients where a a particular treatment might be more successful."

Lizette: So, some of these mutations, are they easier to treat? I know we're going to get into treatment in a little while, but do the chromosomal abnormalities or these mutations lend to some people being treated because of a lower risk versus higher risk?

Dr. Stein: Yeah, exactly. So, some mutations fall into what we call a favorable risk category; and those are the mutations that seem to do very well with sort of standard chemotherapy, where a standard chemotherapy that's been around for a long time is very likely to put that patient into a complete remission. While there are other gene mutations that maybe the standard chemotherapy that we give doesn't work quite as well, and then we think about giving maybe alternative types of chemotherapies.

We stratify people into three risk categories. There's favorable risk, intermediate risk, and unfavorable risk, or adverse risk; and that's how we typically stratify people. So, I'd say, at the time of diagnosis, 15 to 20% are favorable risk. And then, the other 80% of patients fall into intermediate or having unfavorable risk disease.

Elissa: Does that also determine prognosis for the AML?

Dr. Stein: It does. So, patients with favorable-risk disease have a better prognosis at the time of diagnosis than patients with unfavorable-risk disease, as the names sound.

I do think it's important to note the following though, on a more positive note, which is that with the new treatments that have been developed, some of the subtypes of acute myeloid leukemia that were previously considered unfavorable risk have now moved into a better risk category. It's not like these things are static. Like as new treatments come around, the risk categories shift.

The best example of this is a very rare subtype of acute myeloid leukemia called acute promyelocytic leukemia (APL), which, 40 years ago, was probably the least favorable type of acute myeloid leukemia. But we now have therapy for that subtype that is, essentially, 100% effective. And it's now the most favorable subtype of acute myeloid leukemia.

Elissa: That's great.

Lizette: Before we get into the current treatments for AML, would you tell us why it's such a difficult disease to treat.

Dr. Stein: That's a good question. One reason that it's a difficult disease to treat is that there are just subtypes of acute myeloid leukemia that are not responsive to the treatments that we have out there. I think the second reason that it's difficult to treat is because we don't completely understand the biology of all subtypes of acute myeloid leukemia, which means that we're stuck a little bit with treatments that are very general and don't target the specific genetic underpinnings of the disease. We have some subtypes where we can target the genetic underpinnings of the disease, but for many subtypes, we can't because we just don't understand why the disease develops in those subtypes.

Elissa: Right.

Dr. Stein: So, that's number 2. I think the last reason is because the treatments for acute myeloid leukemia, until very recently, have been quite intensive and quite toxic. So, the treatments for acute myeloid leukemia cause many patients to have very low blood counts, which leads to infections, and leads to people really not feeling well.

In addition, one of the best treatments for acute myeloid leukemia is a stem cell transplant, which is a great treatment and works really well. But it's not easy. It's not something that I would say is a walk in the park.

Elissa: Yeah.

Dr. Stein: So, that becomes another reason that I think it's become a little bit tough to treat. And we're, obviously, trying to improve in all of those different realms.

Elissa: Yeah, I think we've seen the cancer treatments, in general, kind of morph where we've got more targeted treatments for a lot of cancers, particularly a lot of different blood cancers, whereas, AML's been a little bit slower. But the last few years have been very good with getting better treatments because it used to be just the standard chemotherapy, just wipe everything out. And let it all grow back.

Dr. Stein: Exactly.

Elissa: But, let's get into the current treatments. So, what are the current treatments for AML?

Dr. Stein: Okay, there are so many. It's hard to talk about them. When I started this, like you just said, there were sort of like one chemotherapeutic approach and wipe it all out and hope for the best and hope that the good stuff comes back.

But now we have a whole bunch of different treatments. To make it relatively simple, I'm going to break it down into just a few categories. The first category of treatment is the same strong intensive chemotherapy we've been giving for many, many years. That is typically what's called 7+3, which is 7 days of a chemotherapy called cytarabine

with 3 days of a chemotherapy called daunorubicin or idarubicin. We still use that a lot for younger patients with acute myeloid leukemia, and I'm defining younger as, I don't know, less than 65, let's say.

Now for older patients, again, older than let's say 65 or 70 with acute myeloid leukemia, which is really the group of patients who are most likely to get acute myeloid leukemia, we have a new lower intensity treatment which is remarkably successful. And that is the combination of a medication called azacitidine, which is an intravenous medication that you get for seven days in a row, with a pill called venetoclax. And that combination of azacitidine and venetoclax, or I'll call it aza-ven, leads to remission in about 70% of patients with acute myeloid leukemia who are older.

And in fact, that treatment is so successful that there are now clinical trials that are comparing this lower intensity aza-ven approach with the intensive chemotherapy of 7+3 for younger patients. So, it may be within the next couple of years, those people who would now be getting intensive chemotherapy with 7+3 inpatient, maybe not all of them, but many of them, even younger patients, may be getting aza-ven as an outpatient as their initial treatment, which I think will be a dramatic change in, number one, the experience for the patients, but number two, how we think about treating AML.

So those are the two big categories. And then, on top of those two big categories, there are the targeted therapies. So, think about the different gene mutations that we talked about a few minutes ago. And, for many of those gene mutations, not all of them, but now for the most common of those gene mutations, we have targeted therapies that goes after the particular mutation.

So, for patients with FLT3 mutations, which are very common in AML, we have targeted FLT3 inhibitors. For patients with IDH mutations, we have targeted IDH inhibitors. We now will likely have a targeted inhibitor for patients with NPM1

mutations hopefully within the next year. And what we've done is layered on those targeted treatments on top of the backbones that I just described a second ago.

Elissa: So, with the 7+3?

Dr. Stein: Exactly, with the 7+3. So, if a patient has a FLT3 mutation, they're going to get 7+3 with a FLT3 inhibitor. If it's an older patient with a FLT3 mutation, there are clinical trials looking at adding on a FLT3 inhibitor to that backbone of azacitidine and venetoclax. And, the last thing I'll say is, we have so many inhibitors now that we're now thinking about combining inhibitors in combination with 7+3. So, I don't really know anything about multiple myeloma, but I do know that they give a lot of drugs together. They give quadruplets and quintuplets, I think they're talking about. And I don't think it's that far away that we're going to be thinking about doing this same thing in patients with acute myeloid leukemia.

Elissa: That's exciting.

Dr. Stein: Yeah.

Elissa: Now, we mentioned in the introduction that you helped develop a couple of new IDH inhibitors. Could you tell us a little bit more about those?

Dr. Stein: Yeah, yeah. So, at Memorial Sloan Kettering, we worked on two IDH inhibitors, an IDH1 inhibitor and an IDH2 inhibitor. Those are drugs that target mutations, either an IDH1 or in IDH2. We worked on the clinical trial that led to the approval of those drugs for relapsed and refractory acute myeloid leukemia. And again, these mutations occur in about 20 to 25% of patients with AML. So that was very exciting. And a lot of our work led to clinical trials that are being done now that are combining these IDH inhibitors with standard of care chemotherapy.

So, there's a large clinical trial on, being run out of The Netherlands, which is combining IDH inhibitors with intensive chemotherapy to see whether IDH inhibitors with with 7+3 are better than 7+3 alone.

Elissa: So, now I want to discuss menin inhibitors, which, as an AML survivor, I'm very excited about. So, could you tell us, for starters, what menin inhibitors are?

Dr. Stein: Yes. So, to know what a menin inhibitor is, we have to talk about two other subtypes of acute leukemia. Now, I'm not even talking about acute myeloid leukemia. I'm just talking about acute leukemia.

Elissa: Okay.

Dr. Stein: So, one subtype is only in acute myeloid leukemia and that's called acute myeloid leukemia with an NPM1 mutation. That's about 30% of patients with AML will have an NPM1 mutation. That's one subtype.

There's a second subtype of acute myeloid leukemia that has a chromosome rearrangement on chromosome 11. That is called a KMT2A rearrangement. That occurs in patients both with acute myeloid leukemia and with acute lymphoblastic leukemia (ALL). And what a lot of scientific discovery over the past 20 years has shown is that the development of NPM1-mutant acute myeloid leukemia and KMT2A-rearranged acute leukemia depends on the interaction of a protein called menin with some other big protein. What it's called is not important.

So, the idea is that if you can take a drug and block the interaction of menin with this other big protein, you can reverse the leukemia and make the leukemia go away. This is a class of therapy, which also exists in the IDH inhibitors called differentiation therapy.

Differentiation therapy is the following. If you go back and think about how we standardly treat AML, the basic idea is you're trying to kill leukemia cells. Okay, so you're giving strong chemotherapy. You're hoping the leukemia cells die and that only the good cells grow back, like we talked about before.

Differentiation therapy is totally different in that what it's trying to do is to take those leukemia cells and rehabilitate them to become normal. So, you're reprogramming a

leukemia cell to turn into a normal healthy adult functioning member of the bone marrow society. Right.

And menin inhibitors are a class of differentiation therapy, as are IDH inhibitors. They're a class of differentiation therapy that can lead to these complete remissions. Now, I like this analogy, so I'm going to tell you about it.

So, as you're getting these cells to differentiate and trying to rehabilitate them, they don't like it. I like using my toddler analogy. It's like you're with a toddler and the toddler doesn't want to go somewhere. You're in Target with them, and they want to look at the toys; and you're saying, "No, we have to leave now and we have to do something different." So, what does the toddler do? They sit down on the floor, and they start screaming and yelling and they throw a tantrum.

So, that's what these cells do when you start to try to rehabilitate them. They start throwing a tantrum. And the way they throw a tantrum is they release substances, what are called cytokines, that can cause the blood vessels to get a little bit leaky and cause fluid accumulation in the legs, in the lungs, and sometimes in some other places. That is an event called differentiation syndrome. So, differentiation therapy aims to rehabilitate these cells. The cells don't like it, and they cause a differentiation syndrome.

The good thing about differentiation syndrome is it's actually easy to shut off. You give a patient steroids, and it gets better. But it's something that we look out for very carefully in any patients who are getting a menin inhibitor, an IDH inhibitor, or, for that matter, a FLT3 inhibitor as well.

Elissa: Okay, so a quick question then with the menin inhibitor. You mentioned that it is essentially giving the chance for those immature cells to become normal healthy blood cells. Is it then preventing any new immature cells that have come in to continue that path?

Dr. Stein: It is. So, it's really targeting at the most basic molecular level the development of those immature cells so that they stop developing and you get what's called terminal differentiation, so that all the bad cells just kind of like become normal and only good cells start growing again.

Elissa: That's great. Now, you mentioned a couple different gene mutations. Is that who currently is eligible, people with those gene mutations to get menin inhibitors?

Dr. Stein: Yep. Well, there's one menin inhibitor that has been approved. Right now it's only approved for patients with the KMT2A rearrangement for relapsed and refractory disease. We anticipate that it will also be approved for patients with AML with an NPM1 mutation. That is hopefully going to happen this year or maybe early next year.

Elissa: Okay.

Dr. Stein: There are other subsets of acute myeloid leukemia, which may actually respond to menin inhibitors; and there are a few clinical trials going on that are looking at these other subsets to see if the menin inhibitors will work.

Elissa: That's great. So, is that given in the first line of treatment, or is this more for relapsed/refractory AML?

Dr. Stein: Yes. So, right now it's approved for relapsed/refractory, but there are many clinical trials moving it up to the frontline of treatment. Right, because the way the development pathway goes, is you have a drug that works in relapsed/refractory setting. You obviously don't want a patient to relapse. Right, you want a patient to be cured from the get-go. So, you take that drug and then you put it into a clinical trial for newly diagnosed AML in combination with something that you know already works with the idea that that's going to lead more patients to be cured.

Lizette: Wow. Well, thank you for explaining differentiation syndrome the way that you did because I could totally relate to a toddler.

Now, I know that we're talking about newer therapies and a lot of our folks always ask us about CAR T-cell therapy. Is there a reason why CAR T-cell therapy is not really available for AML?

Dr. Stein: There is. There's a good reason why it's not available so much for AML, and I'll tell you why. But I'll just tell you that people are working on trying to make it available for AML. I mean it's not like all hope is lost.

But the basic idea is that, CAR T cells, as many might know, are T cells which are a kind of immune cell, a kind of white blood cell that are engineered to recognize a protein on the surface of a leukemia cell, so that that engineered T cell kills the leukemia cell.

So, when you're thinking about engineering a white blood cell to recognize a cancerous cell, what you're looking for is something that is on the cancerous cell that is not on a normal cell. Right, because you want to only kill the cancerous cell. So, in acute lymphoblastic leukemia (ALL), for example, there is something that sits on that acute lymphoblastic leukemia cell that is, perhaps, unique to that acute lymphoblastic leukemia cell; and even if it's not unique, even if you wipe out all of the normal cells with this particular protein, it doesn't hurt the patient.

Now, in acute myeloid leukemia, the problem is that all of the targets that are on the leukemia cells are also on normal healthy blood cells. So, when you give a CAR T cell, it might eradicate the leukemia, but it also tends to eradicate all the normal blood production in the patient's bone marrow. Chemotherapy kind of does that also, right?

Lizette: Right.

Dr. Stein: So, why are CAR T cells problematic? The problem is that with chemotherapy, you know that if you wait a certain amount of time, the regular normal healthy white blood cells will come back, usually after like 25, 30 days. But with CAR T cells, it seems to be that with the current CAR T cells, the normal healthy blood cells

don't come back. So, the only way to make normal healthy blood cells come back is to do a stem cell transplant. So, that is a major issue.

Lizette: Sure. Now, I know that you explained the management of differentiation syndrome. What are the other side effects of all these various treatments, and how do you really manage them?

Dr. Stein: So, I think that the biggest side effects of treatment are low blood counts. So, how do you manage low blood counts? One thing that's very important is to be extremely aggressive with transfusional support, which means that when I'm giving my patients any chemotherapy, I'm checking their bloodwork. I mean, if they're inpatient, they're getting their bloodwork checked daily. If they're outpatient, I'm checking their bloodwork two to three times a week and being very aggressive with giving them blood products and giving them platelets so that they're not having symptoms related to anemia and not having any bleeding issues.

There's an upside and a downside to that. The upside to that is that people don't get really anemic and don't feel bad. The downside is that it takes a lot of time to come into a hospital or clinic two to three times a week and get a transfusion. It's like dialysis. It sucks up that much time. So, that's one issue that comes up.

Nausea isn't a huge issue typically, but we are aggressive about giving people anti-nausea drugs, to have at home just in case they feel nauseous with some of the treatments. Some people can develop mouth sores when they're getting the treatments, so we're very aggressive about mouth care and giving medications to help. It's crazy how, you know, just the littlest- I mean you think about like a canker sore that you get; and it's such a small thing, but it can be so painful and uncomfortable. And those kind of sores can happen as a result of chemotherapy that we give. So, we're very aggressive about trying to prevent those sores and good oral hygiene. So, that's another thing that can happen.

We give prophylactic antibiotics to help prevent infections, so the patients don't end up with fevers and end up in the hospital. That's another very important thing that we do. So, I think those are some of the biggest side effects.

There, there are other side effects that, fortunately, patients don't really notice. So, some of these inhibitors, they can cause like changes to the EKG (electrocardiogram), but a patient wouldn't notice that. It's just something that we notice when we're doing our testing. Sometimes, it can change liver function tests, so we notice that sometimes. But I'd say the lowering of the blood counts is really the biggest issue with all of these therapies.

Elissa: Now, one thing I want to ask about, when I was in treatment with the 7+3, they gave me steroid eye drops. Could you explain those and what those are used for?

Dr. Stein: That's a good question. So, we use those for the consolidation portion of chemotherapy with a high-dose cytarabine-based consolidation. The steroid eye, for reasons that I actually don't know biologically how it happens, but I think what happens is that, when you're getting high doses of cytarabine, it can, I think, leak into the eyes and cause a little bit of of inflammation, which can be just uncomfortable. So, we do give people steroid eye drops in advance of that treatment to keep their eyes from getting inflamed.

There are rare occasions where the steroid eye drops don't work so well. But, I had a pharmacist once tell me that you can actually give ibuprofen eye drops, and those really work really well also. So, that's something that we occasionally have to do.

Elissa: Okay, well that's good to know. And then, a couple other side effects that I wanted to ask about are cytokine release syndrome, which you mentioned earlier. And then also, graft-versus-host disease (GVHD) with transplant. Could you discuss those a little bit and how those would be managed?

Dr. Stein: Yeah, sure. So, cytokine release syndrome, it is something that we see with CAR T cells, but it overlaps with the differentiation syndrome that I talked about before. I think it's all really the same thing, which is that you get these cytokines that are causing inflammation and causing fevers. Cytokine release syndrome and things like differentiation syndrome are primarily managed with anti-inflammatory type drugs. And you can get really fancy with your anti-inflammatories. So, the least fancy way of an anti-inflammatory is steroids. Right, steroids are really great when you give them for a short period of time. They work really well. And then, as cytokine release syndrome might get worse, especially with CAR T cells, we have fancier, more expensive drugs like things that target specific cytokine pathways. Maybe the most common one is a drug called tocilizumab, which is an antibody that targets particular cytokine pathways. So, that is one thing that we do for cytokine release syndrome. And then GVHD. So, that becomes a little bit of a different discussion. Before we were talking about just the treatment for leukemia. We didn't really get into the transplant part of it yet. But as people who are listening likely know, a lot of times we're doing stem cell transplants for our patients with acute myeloid leukemia. And after you do a stem cell transplant where you take donor stem cells and infuse them into the patient to essentially create a new healthy blood system for them, patients can develop what's called graft-versus-host disease.

The graft are the stem cells from the donor. Okay, so when you infuse, the stem cells from the donor into the patient or the host, those stem cells sometimes look around when they get inside this new body; and back to my toddler analogy, they say, "I don't want to be here. I don't like it here. I'm going to try to cause problems because I'm angry." And graft-versus-host disease is where patients can develop most commonly a skin rash or other rashes, sometimes some diarrhea or nausea. Occasionally, but rarely, it's some liver abnormalities because the donor stem cells are attacking the body of the host.

There are many treatments to, number one, help prevent the development of graft-versus-host disease and, number two, if it does develop, to treat graft-versus-host disease. All of these treatments tamp down the donor stem cells from being too aggressive. It's saying, "Okay, we understand you're unhappy, but we're going to learn to live in this body slowly but surely, you're going to get used to it, and eventually you're going to be fine." And there have been a whole bunch of therapies that have been approved over the past few years that really keep graft-versus-host disease from becoming too active.

Lizette: And just talking about stem cell transplantation, with some of these newer medications that we've been talking about, do you see some people not going towards transplant at this time?

Dr. Stein: Such a good question. So, I always tell my transplant colleagues that, in some ways, my job is to put them out of business. We all want to come up with therapies that are easy for patients to get and where you don't need a stem cell transplant because it's tough to get a stem cell transplant. I mean think about a disease like chronic myeloid leukemia (CML) where, many years ago the treatment for that disease was a stem cell transplant. And then, researchers, Brian Druker and others, came up with these amazing pills, these tyrosine kinase inhibitors that put the disease into remission. Now, it's very, very rare for a patient to get a stem cell transplant for chronic myeloid leukemia.

So, I think that these treatments that we have now, I hope, one day will lead to an era where maybe we can avoid a stem cell transplant. Having said that and not to throw too much shade at my stem cell transplant colleagues, I'll say a couple of other things. Okay, so number one is, stem cell transplants are getting safer. They are much safer now than they were 30 years ago because we have better treatments for graft-versus-host disease and because pretty much everyone has a donor now, because we can do these half-match haploidentical transplants without too much of a problem. So, that's number one.

Number two, is the downside of these small molecule drugs that I talked about is that they're really good at getting patients into remission. But the problem is that as single agents, the remissions tend not to be durable. Meaning that if I've got a patient with relapsed and refractory acute myeloid leukemia, and they're eligible for a menin inhibitor and I give them a menin inhibitor, it's got a really good chance of working and putting them into remission. But the chances of that remission lasting more than a year are not super high. So, the role for these drugs, at least now, is to get patients into remission and then get them to a stem cell transplant as quickly as possible, which will hopefully be curative.

Elissa: That's great. So, that is a great segue to talk about the future of AML-

Dr. Stein: Oh, the future.

Elissa: -treatments.

Dr. Stein: Great.

Elissa: So, are there any emerging therapies or those in clinical trials that you're particularly excited about?

Dr. Stein: Yeah, I think what I'm most excited about right now are these combinations of drugs that we talked about, taking drugs that are already approved and combining them together to improve the remission rates. I think that's something that is really exciting, and I think moving some of these targeted therapies up front for newly diagnosed patients and then combining drugs to make that treatment more effective is where the field is going over the next few years. So, I think that is really exciting.

I think the idea of giving patients lower intensity therapy with azacitidine and venetoclax, even if they're younger, and avoiding them needing to be in the hospital to get 7+3 is also really exciting. I think that will make a dramatic difference in the lives

of patients. Although the people who get it won't know it because they never will have experienced the 7+3, but I think that will make a dramatic difference.

There are other drugs that are being developed that are in clinical trials now that I'm excited about. There are drugs that target a pathway called the CK1-alpha pathway, which I think are very, very exciting. There are drugs being developed for a subset of acute myeloid leukemia that has mutations in genes called splicing factor genes. So, there's a lot of research being done in that area. Splicing factor mutations account for probably 20-30% of patients with acute myeloid leukemia. So, there are opportunities there.

I do think we are at a little bit of an inflection point though in the following way. The way these things happen is they sort of come in waves. So, there was research on IDH inhibitors; and then clinical trials for IDH inhibitors. And now we've got an approval. And then the same thing happened with FLT3 inhibitors. The same thing happened with menin inhibitors. I think we're in that period right now where there's a lot of basic science research being done to identify what the next best target is-

Elissa: Right.

Dr. Stein: -for which we're going to have drugs for clinical trials that will hopefully then lead to another approval or two or three.

Elissa: Three would be nice.

Dr. Stein: Three would be nice, yeah.

Lizette: Now, we keep hearing about bispecifics. Do bispecifics have a future in AML?

Dr. Stein: So far, they have not had much of a future in AML. I think the problem is that, part of the issue here is that, and this is also the issue with CAR T, is that the drugs are tested initially in patients with relapsed and refractory disease. And in

patients with acute myeloid leukemia, it's just hard to do trials in patients with relapsed and refractory disease. So, I think that's one of the issues.

I think maybe the place for bispecifics is in earlier lines of therapy where patients maybe haven't relapsed yet. Maybe you can use it instead of consolidation chemotherapy. I mean that might be an interesting thing to do. So far, the bispecifics that have been developed have not actually really gone anywhere.

Elissa: Is again the problem finding that right target?

Dr. Stein: Yeah, a lot of the problem, just like before, is the target. So, bispecifics are very similar to CAR T cells. And again, yeah, like you said, the issue is the target. The targets are also expressed on normal healthy cells, so you get a lot of side effects.

Elissa: Are these still in trials though? Are they still potentially looking to see if this might work?

Dr. Stein: They are. So, no one has given up on CAR T-cells. No one has given up on bispecifics. I think though there's a lot of tweaking that needs to be done, so it's not a slam dunk like some of these other drugs were true slam dunks when you started giving them to patients.

In cancer in general there are the following ways to think about stuff. There are drugs that you know the minute you give it to someone that they are remarkably effective. I mean getting back to CML and giving a patient Gleevec® or imatinib, that was clear. The first patient who got that drug, it was clear that this was going to be a blockbuster.

Elissa: Yes.

Dr. Stein: But then there are other drugs where you need to play around with a little bit of trial and error and see what's the best way to give it, who's the best patient to

give it to. I think that's where we are right now with the bispecifics and with CAR T cells.

Lizette: So, really continuing this conversation about AML research, you mention that you think we may be headed to adding more targeted therapies onto already established therapies and really looking into finding more therapies for more of the mutations. When do you think this'll be accomplished?

Dr. Stein: Well, I hope in my lifetime. I mean, I think that it's going to happen sooner rather than later. When I was in medical school, even in residency and when I started my fellowship, there were basically no treatments for AML. There was 7+3 and chemotherapy like 7+3, and that was it. And then in my career, which is now, I don't remember, maybe 15 years old.

Lizette: You're just dating yourself.

Dr. Stein: Yeah, I know. I can't believe I've become like an old man. It's so depressing. So, in any case, we've had all these approvals, right? Seven, eight approvals. And that's because the science has gotten a lot better.

So, I think we're going to have many more approvals in the next five years because the tools we have to understand the biology of these diseases are so much more powerful than they were 40, 50 years ago. So, I really am hopeful that by the end of my career, whenever that might be, we're going to be able to cure the majority of our patients with AML. I mean, obviously, I want to cure all of our patients with AML. But I really believe that that's going to happen.

Lizette: And you see right now in present day that quality of life has been changed for patients with AML.

Dr. Stein: Oh, 100%, 100%. The fact that we can give AML treatment outpatient now is a huge change in quality of life. There is no one who I have met in my practice or thinking about it if it was me, who wants to be sitting in a hospital for a month? No

one likes being woken up in the middle of the night to get vital signs and getting stuck for labs. And, if you can treat patients in their own home, that's a major quality of life issue.

Elissa: So, that's a possibility for induction treatment?

Dr. Stein: I don't know about induction treatment. More like lower dose therapy, like with aza. So, if we replace induction with aza-venetoclax, then 7+3 will fall by the wayside and we won't need to admit quite as many patients.

Elissa: That's great. Yeah, I remember when I was in treatment, I was one of the few people who had done outpatient for consolidation treatment. And I think they didn't know what to do with me, but I lived so close to the hospital that it was easy for me to do. But it made such a difference to not have to check into a hospital for a week every month.

Dr. Stein: Yeah, and we actually have this program now at Sloan Kettering. I think some other centers are doing it also where, for consolidation, we actually send patients home with an ambulatory pump to get their chemotherapy. And it works really well. You may have experienced something like this that, you know, you're in the hospital for a month; and then I say to the patient, "Okay, we're going to give you this next chemotherapy at home." And people get really nervous about that because they're like, "Oh, you were watching me so closely." But I would say universally, once the patient gets the chemotherapy via the ambulatory pump at home, they are comfortable and are much happier than that didn't need to come into the hospital.

Elissa: Yeah, yeah, definitely.

So, our final question today, now we've talked about all these wonderful things. So, 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 AML?

Dr. Stein: Number one, I think it's always important to maintain hope. I think that psychology does influence how you handle going through the treatment journey, and remaining hopeful is a piece of that. I don't want to pretend it's always easy to remain hopeful. It's not. And some people have a harder time than others. I actually think it's really important if you're having a hard time maintaining hope to talk to your doctor, your oncologist, to talk to a psychologist, to talk to a psychiatrist, or a support group. There are ways of training your brain to maintain health.

From a biological perspective, people should maintain hope because the treatments we have for acute myeloid leukemia are so much better than they were when I started doing this. We have so many new things that we can do that are more effective than they were 15 years ago. We can get many more patients to a stem cell transplant. It used to be you could only have a transplant if you had a sibling who was match. And now that's totally not true. Over the past five years, eight years, I don't think I've encountered a patient where we couldn't find a match for a transplant.

So, all of those things are extremely hopeful. And the other thing that is extremely hopeful is that science continuously advances. And over time, there are going to be new discoveries made and we are eventually going to get to a point, hopefully really quickly, where we're able to tackle and cure all acute myeloid leukemia. I firmly and truly believe that.

Elissa: That is so wonderful. I mean, it's so true how fast research has gone, particularly in these past few years. It seems like 2017 was kind of the magic year where it just exploded forward. I was diagnosed in 2016, and all there was was 7+3 or transplant. Those were the options, and they were looking into a few additions, but that was it. And so, it is so exciting to see all the new treatments that have come out and really targeting these more difficult gene mutations to try to give hope to these patients.

Dr. Stein: And the last thing I'll say is that, I do think it's important that research continues to be done and basic science research continues to get funded because it might look like the research that's being done, well what does doing research on a worm or on a mouse have to do with treating acute myeloid leukemia? But a lot of the discoveries and the treatments that we have come out of understanding really the basic biology of these diseases. And that's why the funding of research is just so important.

Elissa: Absolutely, and we're still working on that on our end to try to keep research funded and hopefully patients, as well, will also enter clinical trials. And we have a Clinical Trial Support Center. We'll have information in the show notes, so patients can enter clinical trials and help to advance research but also put themselves in line for a different treatment that could work really well.

But thank you so much, Dr. Stein, for joining us today and talking all about AML and the new exciting treatments that are here or coming down the line, and so, we really appreciate you being here with us today.

Dr. Stein: Thank you so much for having me. It was really a pleasure.

Elissa: Thank you.

Lizette: Thank you.

Elissa: And thank you to everyone listening today. *The Bloodline with LLS* is one part of the mission of The Leukemia & Lymphoma Society to improve the quality of lives of patients and their families.

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