

## THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

### ***Episode: 'Complexities of Secondary AML with Dr. Goldberg'***

#### **Description:**

Join us as we speak with Dr. Aaron Goldberg from Memorial Sloan Kettering Cancer Center in New York City. Dr. Goldberg discusses how secondary AML differs from AML and how treatment is determined. Secondary AML is a diagnosis of AML that has occurred after previous exposure to radiation or chemotherapy for another cancer or has evolved from a prior diagnosis of MDS, MPN or Aplastic Anemia. In this episode, Dr. Goldberg points out the major difference between secondary AML and de novo AML and new, promising treatments.

#### **Transcript:**

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

**Edith:** I'm Edith.

**Lizette:** And I'm Lizette. Thanks so much for joining us on this episode.

**Alicia:** Today we will be speaking with Dr. Aaron Goldberg. Dr. Goldberg is an Assistant Attending Physician at Memorial Sloan Kettering Cancer Center in New York City. Dr. Goldberg cares for leukemia patients, leads translational research projects, and serves as the principal investigator for multiple clinical trials. His research interests focus on the development of novel therapeutic approaches for acute myeloid leukemia, including combination therapies to target residual disease as well as evaluation of real-world outcomes of current therapy and genomic predictors of response.

Welcome Dr. Goldberg.

**Aaron Goldberg, MD, PhD:** Well thank you very much. It's a real pleasure to be with you today. This is my first podcast, so I'm very excited.

**Lizette:** Wow!

**Alicia:** Yay! Well, we're happy it's with us.

**Dr. Goldberg:** Excellent, excellent.

**Alicia:** We're really excited about the conversation here today, which will be about secondary acute myeloid leukemia, also known as AML. But before we jump into that, we'd love to get to know our guest speakers a little bit more, so what brought you to the field of medicine, specifically hematology and oncology?

**Dr. Goldberg:** Sure. So, I've actually been interested in medicine really for almost as long as I can remember. I grew up in Texas, in San Antonio, Texas, and there was no one in medicine in my family; there were no doctors. But at the same time, like so many families, our family had serious experiences with illness. So, I always grew up hearing stories about my, my two grandmothers.

So, when I was around a year old, a little baby basically, both of my grandmothers had cancer. My dad's mom had breast cancer and, unfortunately, it was metastatic breast cancer. And my grandpa, my, dad's dad, he's a pharmacist and closest person to medicine in my family. And he's an incredibly smart guy, and he brought her basically everywhere; to, you know, the NIH and Sloan Kettering for clinical trials and, unfortunately, in that era, there really was not much. And so, she, tragically died, when I was a, a year old and I never got to know her. And by all accounts, she was just this remarkable person.

Around that same time, my poor parents are dealing with this, my mom's mom, also had cancer. She actually had lymphoma, so a blood cancer of the lymph nodes, and she was incredibly ill. And she got chemotherapy and, I heard stories about how her hair fell out and she had nausea, and everyone thought she was also, tragically going to die.

But, remarkably, she achieved a remission and really was probably cured because she never had any evidence of lymphoma coming back, which is pretty amazing particularly given this was so long ago and the types of treatments that were available then are not nearly as good as they are now. But she lived 27 more years and she lived with us pretty much, very frequently as I was growing up and was a really important part of my life. And so, I certainly was, struck by that knowing one grandma growing up, the impact that having an effective treatment, can have on a person, on a family.

And then, finally, one of my interests in science was also, I think, kindled by my uncle on my dad's side. He actually had HIV and AIDS, and this was in an era really before there were really effective therapies, and so when I was 14, he tragically passed away. I knew him, well, and he was just this amazing just vibrant man. He was actually, an actor and singer and then eventually a Hollywood talent agent, and just this amazing guy. So, there are actually all kinds of, now famous actors who he sort of brought into the movies and just this incredible person.

And I always think about the fact that if he had lived just three more years, until 1996, you know, when combination antiretroviral therapy was really put in common use in HIV, he would probably be alive today. And so I think it really speaks to the urgency and the importance of research and what we're doing both in the clinic and also in the laboratory to develop new treatments for patients because the time is now and, really it's critically important that we have better therapy. So, that's what sort of I think drove me into both medicine and to science.

So, in high school I went to this very nerdy high school. It was actually a big surprise to everyone virtually a public magnet high school called Health Careers High School, believe it or not, in San Antonio, Texas. And so, everyone and someone was interested in some kind of a health profession. And then I went onto college and I studied history of science, and I sort of new at that point I really wanted to be a doctor

and a researcher. And then I, really totally nerded out and went for an MD/PhD program 'cause one doctoral degree was not enough. And so-

**Alicia:** It wasn't good enough.

**Dr. Goldberg:** -right, so all the rest of my friends were going on to like actual jobs, I was still in school. And they're like, "Really, you're still in school?" "Yeah, I'm still in school." It was just like the 25<sup>th</sup> grade or 32<sup>nd</sup> grade or something like that. Yeah, so it was a nine-year program, so four years in medical school and five years in the lab. And I loved it. It was just really a time to really immerse myself in medicine and science. And I have to say I really enjoyed it even though it was a long program.

And I also want to speak to the importance of, having really great mentors because I think that, you know, mentors really were so important to bringing me to where I am today. So, just out of high school I worked for a summer already in a lab, actually at MD Anderson cause I'm from San Antonio so I was, Houston was only three hours away, and so I worked at MD Anderson for a summer and worked in the laboratory of this scientist named Dr. Sen Pathak. And he's an expert in chromosomes.

And I have to say to this day what I learned in that lab I still think about even as I see patients because that's where I learned how to actually look at chromosomes under the microscope. I mean they drew my blood and we grew my cells in the lab and then, you know, put my chromosomes on a dish and looked at them under the microscope and that's how I sort of got a sense of what that actually, means and what the effects are of different treatments and therapies on these cells, and I went on and did work in similar labs at college.

And then in graduate school my mentor was a just an amazing scientist named David Ellis. And so, there's where I really pursued this fascination with how cells regulate their genes. You know, cells have this amazing, this instruction book of the genes that really tells the cell what to do. But, obviously, a nerve cell is very different than a liver

cell, very different than a muscle cell but why is that cause it has the same dictionary? So, it's different because it reads different parts of the dictionary.

And so that's where I sort of really explored how cells turn on and turn off different genes in a very basic way, at some level thinking that was kind of far removed from cancer, but it turns out that a lot of what we learn collectively in a lab about very basic biology is so important for how cancer cells work. So that was incredibly valuable.

And then, leukemia, I think, for me is the perfect kind of field because it really brings to bear not just, you, don't have to have just a deep understanding of the science but you also have to be, I think a really truly caring person. And so, I worked with Rich Stone, who you may know, at Dana Farber who really encouraged my interest in leukemia. And now, most recently, my mentor is still Marty Tallman here at, at Sloan Kettering. And I, was in his clinic and he taught me how to basically how to write and run clinical trials and how to take care of leukemia patients and how to be a good leukemia doctor.

So, that's sort of been my journey to being a leukemia doctor. And I think my general approach is that I always try to treat every patient as if they were a member of my family.

**Alicia:** That's awesome.

**Dr. Goldberg:** Yeah. To, just to see them sort of, you know to talk to them and, to give them the advice that I'd want my family member to hear. And really my goal is to really use a better understanding of the science and the biology to give each and every patient, the best chance to having a, good outcome. And so that's how I got to where I am.

**Alicia:** That's incredible, and I think it's, when you're going through certain experiences, you're never really sure why until you-

**Dr. Goldberg:** Yeah.

**Alicia:** -are able to look back on, you know, the combination of things and say, "Wow, okay, all of that brought me here." So, it's so awesome to hear your story and see where it brought you to and the families that you're helping.

**Dr. Goldberg:** Thank you, yeah. It's a privilege honestly.

**Alicia:** Right. So, as I mentioned earlier, we're going to be speaking on this episode about secondary acute myeloid leukemia, but before we get into that diagnosis specifically, what is leukemia?

**Dr. Goldberg:** Yeah, so, obviously, we'll start there at the beginning what is leukemia? So, leukemia is a blood cancer. It's a cancer of the blood. You know, it literally means leukemia white blood cells, you know, so white blood. And, cancer, of course can arise in various parts of the body. Some patients have prostate cancer, some have breast cancer. This is fundamentally a cancer of the blood and really of the bone marrow.

The bone marrow, the sort of liquid part within all of our bones, is really the factory for the blood. And so, the bone marrow makes all of our blood cells. It makes the white blood cells that fight infection, it makes the red blood cells that carry oxygen, and it makes the platelet cells, and those are the cells that help us to clot. And so, the bone marrow is the factory for all, parts of the blood, but the bone marrow cells themselves can also develop into a cancer.

And so when a very early kind of a baby blood cell in the bone marrow gets sort of stuck at a very early stage of development, what it should do that baby blood cell was to differentiate, to grow up and become a more mature white blood cell or red blood cell or platelet. But when a baby blood cell acquires a genetic change, and I would call that a mutation, a change in the DNA, sometimes those changes can make that cell grow more than they should and sometimes those mutations could make that cell fail to grow up and fail to become more mature cells, and so they get stuck as baby blood cells. And when these very immature baby blood cells get stuck and they fail to grow

up and they make more copies of themselves and they grow and they start taking up space in the bone marrow, that's what eventually can become a leukemia.

Patients even might hear this term called blasts. So, you know, they always ask me, "What, is this, doctor? What, is a blast?" So, what is a blast? A blast is the sort of scientific term for an immature baby blood cell. And we all have them, in our blood and bone marrow. In the blood they're usually not detectable. Usually there's so few of them in the blood itself that, they're hard to find, but in the bone marrow, we should be able to see them under the microscope, but they should be still few in number. They should be less than 5% of the cells in the bone marrow should be these baby blood cells called blasts.

The fundamental problem, as I was saying, in leukemia, is that these baby blood cells, these blast cells they get stuck. They don't grow up to more mature cells. They divide and make more copies of themselves and so they start to accumulate. And so, once the blast number goes up to 20% or more of the cells in the bone marrow or in the blood, that's, by definition, an acute leukemia, cancer of the blood.

And then if you look at this type of cell that is making up this blood cancer, then you can tell whether it's an acute myeloid leukemia, as we're talking about today, or an acute lymphoid leukemia, which is a different type of leukemia. But fundamentally this is a blood cancer.

And I think it's important also for everyone who's listening to know that there are lots of different kinds of leukemia also. Some leukemias are actually chronic diseases, so not the kind of leukemias we're talking about today, but it's still the same term. I also see patients with some chronic leukemias like chronic lymphocytic leukemia. And those patients, you know, may even go their whole lives without needing any treatments. It's still a cancer of the blood but it just behaves very differently.

And acute myeloid leukemia, the acute leukemias, in general, is implied by the term acute, they often come to attention more quickly – not always but typically – and they often cause, you know, more immediate problems.

So, I guess coming back, to the question also so, what is secondary acute myeloid leukemia, so what I talked about before was just sort of, in general, leukemia is a cancer of the blood. Secondary acute myeloid leukemias, which is what we're talking about today, represents about a quarter of all acute myeloid leukemia and what that really is that in many cases, we have to say to our patients, "We don't know why you have this leukemia. We don't know why you got it. We don't know why your bone marrow cells acquired these genetic mutations."

With secondary acute myeloid leukemia, we actually often have a better sense, and that's because secondary AML really refers to acute myeloid leukemia, a blood cancer that's come from either an earlier blood cancer, a cancer of the, the bone marrow, such as a, a myelodysplastic syndromes or myeloproliferative neoplasm. So, these are also sort of more low-grade slower kind of blood cancers that have the possibility of progressing over time to a more aggressive blood cancer that we're talking about today in acute myeloid leukemia. And if the acute myeloid leukemia comes from preceding either MDS, or MPN, myelodysplastic syndromes or myeloproliferative neoplasm that turns into or progresses into an AML, then we call it a secondary leu-, acute myeloid leukemia.

And the other form that's really important to know about of secondary acute myeloid leukemia is actually what we call therapy related. So this is, you know, just an unfortunate just a disease where patients who have another kind of cancer entirely, let's say, for example, a woman with a breast cancer who needs chemotherapy and radiation, for example, and that aggressive chemotherapy is really important in the context of the breast cancer to try to keep that breast cancer from coming back. But, for certain types of that chemotherapy, rarely, you know, maybe half a percent of the patients or less or slightly more but around, less than 1% of the patients, that



chemotherapy can actually damage the bone marrow and in a way that actually leads to the development of a different cancer, in this case leukemia. And that could be a therapy related MDS that then develops into leukemia or directly into therapy related leukemia.

And so, a fundamentally secondary acute myeloid leukemia is, again, maybe about a quarter of all acute myeloid leukemias. They either come from, you know, previous blood cancers or from patients that have been treated with previous therapies.

**Lizette:** Now AML, acute myeloid leukemia, is already difficult to treat. It's, an acute leukemia, like you mentioned, you know, very aggressive. Now being that it's secondary AML is it more aggressive, less aggressive, and is it treated differently than somebody that had AML, a *de novo* AML, which is AML without something occurring?

**Dr. Goldberg:** Without a clear previous blood cancer or without like a history of a particular therapy. Yeah, so great question and really important. You know, is there a difference in terms of how aggressive it is and how we treat it and how likely it is to respond to therapy?

So, it can be equally aggressive, I would say, when it comes to attention. You know, that it can result in low blood counts in the red blood cell to the platelets and people can feel weak or they could be prone to bleeding or they could have low white cells and be prone to infection. And so, it can come to attention, and be equally sort of aggressive appearing on presentation. But I think the major difference between secondary AML and *de novo* AML is not so much in the way that it presents but in the way that it responds to treatment.

And so what we know of is that *de novo* AML, as you said, sort of arising, anew from, you know, almost from no clear sort of cause tends to respond a bit better to our older and more intensive chemotherapy treatments. And those are treatments that target really rapidly dividing cells. And so, the other types of, *de novo* AML tends to, be more likely to go away, to achieve what we call a remission, and to be more likely to

potentially stay away with just chemotherapy. And if it stays away forever, then the patient is cured.

Secondary acute myeloid leukemia, in particular, AML that comes either from a preceding MDS or a myeloproliferative neoplasm or is therapy related, is, unfortunately, less likely to respond to our intensive treatments, at least the older treatments, and less likely also to stay away forever just with chemotherapy alone. So we worry in our patients with secondary AML that even if we, they achieve a really good response with chemotherapy, we worry that, fundamentally, there may be some of those cells that could be resistant and still come back later, which is why we think about other therapies and that's, you know, stem cell transplant. And we can talk about that for sure.

**Lizette:** So, because you think that it may come back or it may not respond as well, are you leaning towards more aggressive therapy for these patients?

**Dr. Goldberg:** Yeah. It's a great question. So I think that the treatment for a patient with AML, in general, and secondary AML, in particular, you know, really, it really depends upon who the patient is, who I'm seeing, in the clinic. Who is this patient in front of me? How old are they? How healthy are they besides the leukemia? And what are the goals of treatment?

So, what I always try to do whenever I see a patient in front of me is, I always think is there any way that I can cure this patient, right?

**Lizette:** Um-hmm.

**Dr. Goldberg:** Is there some way that I can get this leukemia under control and then have it stay away forever? 'Cause that would be ideal, obviously, and that would be the, the best goal of treatment.

And sometimes that is achievable. We can sometimes do that and that's, I think, one of the reasons why I love this field is that even with this, very aggressive, as you say,

disease that can be very serious, we still cure some of our patients, and more and more I would say as we have developed better and better treatments. Not everyone though, unfortunately, of course, can be cured of this disease. And the type of treatment and the path that I recommend for the patient really depends upon how healthy they are, how old they are, and what our goals are.

So, the other thing I would, say is that when we treat our patients it's really a team effort. It's not, by no means for sure not just me or the doctor sort of sitting there and doing everything. It's an unbelievable sort of team sport that's working, both in the clinic with the patient behind the scenes to give the best treatments. You know, the nurses, the pharmacists, the advanced practice practitioners, the NPPs, the nurse practitioners and physician assistants, just a whole team of people trying to help and each of us playing our own individual role.

In terms of the treatments, the first thing that we would try to do with a treatment is to achieve what I would call a remission. So, patients say, "Well what is that?" "What is a remission? What does that mean?" So a remission really means that as when I talked about those blasts, you know, in the bone marrow being above 20%, remission would mean that we get those blasts down to less than 5% in the bone marrow. And not just that. A true complete remission also means that I'm able to help the patient recover their good blood counts.

So whereas before maybe they had very low platelets, they were prone to bleeding; maybe they had, you know, anemia; maybe they had low infection fighting cells, they were prone to infections; I want their infection fighting cells to be up and basically to near normal and their platelets also to be up and near normal on their own for me to really say that I've achieved remission.

But then the question is how to keep a patient in that remission, and that really depends upon, again, the goal of treatment. For secondary AML I worry that if I treat the patient with chemo alone, I worry the chemo will may be less, you know, likely,

unfortunately, to truly cure the patient and the most likely way to truly keep the disease away forever would be to consider the possibility of what we call a bone marrow or stem cell transplant, which we can talk about, but that carries with it a lot of risks.

**Lizette:** Sure, definitely. And I know that most of our folks with MDS, myelodysplastic syndromes, are more advanced in age. So, does that mean that people with secondary AML are also advanced in age which would make a transplant more difficult?

**Dr. Goldberg:** This is a great question. I mean the answer to that question, is yes. More often these patients are older and they also might have other medical problems, and they also might have problems that were effects of, if it was therapy related leukemia, they might have effects of the previous treatments from their other cancer. So, you're right, it's a population of patients who are often older and who have been through a lot.

But that said, we actually have some increasingly more effective therapies for our patients with secondary AML, and I would say that age alone is not the most important factor, while it is very important for sure. We used to say, for example, you know, not too long ago, that a patient who was 72, oh, that patient probably could never get a stem cell transplant. You know, that would just be too toxic for the patient. But, what we know now is that it's really not just about the patient's age but really about how healthy they are, what are their other medical problems, what's the function of their organs, you know, the kidneys, the liver? And so, I've taken, you know, many patients through chemotherapy and, oh, other therapies to a stem cell transplant even in, into their 70s. And so, I think that age alone is not the most important factor, but it is really important.

**Lizette:** Sure. And starting treatment, the folks with secondary AML start the same type of chemotherapy regimen as, as folks that don't have secondary AML that have the *de novo*?

**Dr. Goldberg:** Great question. So until recently, the answer to that question was yes and that was not a good thing because we know that, as I said that, unfortunately, patients with secondary leukemia, acute myeloid leukemia, don't respond as well. Their disease, I should say, does not respond as well to the treatments that we were using for years.

I mean I should say also, you know, we're so lucky right now. I feel very lucky to be practicing in a time where we have so many, all of a sudden, new treatments for leukemia and acute myeloid leukemia in particular. For many years, this was sort of a wilderness and even, you know, when I was in medical school, not that long ago, it really was just the same treatments for everybody. All you could get was intensive chemotherapy that is just, it's fundamentally a toxic chemotherapy that kills rapidly dividing cells. And so that means that it has a lot of side effects, obviously. It can kill not only the cells that are leukemia cells, but it also can affect the lining of the gut and the mouth and it can affect the heart. And so it's not something that patients with other medical problems and in age really does play a factor there, you know, patients who were in their 70s, certainly 75 and older they couldn't get those treatments. And as you pointed out, leukemia, AML, in general, and secondary AML, also, is more common in older adults, so what did we have? We really didn't have that much.

And so, we basically had this, literally the same treatment, we call it seven and three. Seven days of a chemotherapy called cytarabine, three days of a chemotherapy called idarubicin or daunorubicin and it was the same thing that we used for all patients regardless of the subtype of leukemia for 35 years.

Now, more recently, we actually have a number of treatments that seem to be more promising. And one is more, definitively more promising than 7+3 for patients with

secondary AML. So we know that the cells, the leukemia cells in secondary AML seem to have these mechanisms, that allow them to be resistant to chemotherapy, so they might be knocked down but there will still be too many of them that will survive and, therefore, the disease remains.

So, there's been a lot of work in the laboratory to try to optimize different types of chemotherapies. And so, one of them that now is an FDA approved treatment specifically for secondary AML and specifically for patients who are fit enough to tolerate our intensive chemotherapies, in general, this is a treatment that's called Vyxeos.

So, what is Vyxeos? So Vyxeos is the same kind of chemotherapy, daunorubicin-cytarabine, but it's actually encapsulated in a little, basically a little fat globule called liposome.

And what's been shown in the lab is that when you have a certain ratio of the, the drugs that are used inside this little liposome, and you encapsulate them in this liposome and deliver them to the patient. Those drugs remain in the bone marrow because of the fact they're in this little fat globule for a little bit longer. And that kind of prolonged exposure to the specific ratio of these drugs seems to be, in the lab and now in the clinic, more likely to kill off these, specifically these forms of secondary AML that seem to be more resistant to standard chemotherapy.

So there was a randomized study now that was led by Jeff Lancet that compared the outcomes of 150 patients basically with secondary AML who got the standard 7+3 and 150 patients who got the Vyxeos, a little over 150 in each arm, and there was a clear benefit. The patients who got the Vyxeos lived longer and, in particular, which was, you know, unheard of because now – we didn't have anything like that before and so this was, you know, the first new drug that was developed, really, specifically for secondary AML, and so that was really important.

But, also, when they looked specifically at the patients who were bridged to transplant and, you know, not everyone was able to be bridged to transplant, but for those patients who were, there was even stronger and clearer benefit. And so, whereas, tragically, unfortunately, most patients with secondary AML were really dying of their disease before. And even now, I would still say, unfortunately, many patients still do die of their disease. For those patients on this study who were able to be bridged to get from this Vyxeos chemotherapy to stem cell transplant, around 70% of them are still alive at a year and close to that, even at two years.

So not all the patients, of course, were able to get there, but it's incredibly promising that we have a treatment now that is better than our previous therapies and that's been shown in a randomized study. I would say that it's not a walk in the park.

**Lizette:** Sure.

**Dr. Goldberg:** So, this is a marathon. Any leukemia treatment, I would say, is really a marathon not a sprint. And so just like the, the other old 7+3, this is a treatment that is generally given in the hospital. We have a program here where we give the actual chemo the first week of it, if the patients are healthy enough, outpatient but then we still hospitalize everybody starting in the second week because that's when things can start to happen to the patient.

So, what could happen? So, the chemotherapy is given, you know, by vein in the hospital or in the outpatient clinic and then the patients go to the hospital. And the patients usually get a catheter inserted in their arm. It looks kind of like an IV when you look at it but actually is a long tube that snakes kind of all the way in through the arm into the big vein in the top of the chest.

And so, they get this, this chemotherapy and that's given, you know, maybe Monday, Wednesday, Friday, for example the Vyxeos as opposed to seven days in a row. And initially patients say, "Hey, doc, that was fine. Nothing really happened. I feel great." Or maybe they had some nausea, and they say, "Well, I had some nausea. And you,

you treated me with anti-nausea medications but that wasn't that bad." But then the second and third week kind of roll around and they say, "You know what, you really did give me some chemotherapy," because it turns out that that's really when we start to see more of the side effects.

So, the side effects that we worry about the most really are that it really knocks out even the good cells for a time. So, I and the patients always say to me, "Well, wait a minute. You're trying, you're telling me that I'm coming with bad blood counts or low blood counts and you want to make my blood counts better, but you're going to make my blood counts worse."

**Lizette:** Right.

**Dr. Goldberg:** So how is that helpful? But the idea is that even though it seems to be better for secondary AML than before, it still is affecting even the good bone marrow cells as well as the leukemia cells. But the idea is that we hope that in many patients that the leukemia cells will be more affected than the good bone marrow cells. And so, in about two weeks we'll see sort of the low points and then we'll often repeat a bone marrow biopsy at that time, two or three weeks, to make sure that the leukemia is going away. If it's not fully going away, we may give some additional chemo to try to get it into remission. But often we'll say, "Oh, looking at that second bone marrow, it looks like the leukemia is mostly gone." And then we just wait.

So after about, you know, two weeks, everything will be low but then after about two or really three more weeks, and really it's about this chemotherapy, as I mentioned, the Vyxeos hangs around the bone marrow a little bit longer, so it takes about five weeks really for blood count recovery. So that's a month in the hospital for our patients. And so, I always have to tell them upfront, you know, "This is a commitment."

**Lizette:** Right.



**Dr. Goldberg:** And it's risky. You know, there are toxicities, as I mentioned, the risk of infection, we worry that there could be bacteria that get in the blood. But that's why they're in the hospital being monitored. If they get a fever, we s-, draw a culture, we start them on antibiotics, and we get them through it. And we really take a one-day-at-a-time-approach, but the idea is then the blood counts come up. Ideally, we do another, we, we can get them out of the hospital, do another bone marrow biopsy, and then really show that that patient's achieved a remission, good blood cells counts, blast less than 5%. And then the question becomes what do we do next?

And that's where we should talk about bone marrow transplant. So, bone marrow transplanters, stem cell transplant is not something that we say a patient must have. One of my mentors Sergio Giralt, who's the chief of our transplant service, he likes to say that transplants, bone marrow transplant, stem cell transplant is never a requirement. It's a decision that a patient sort of comes to in consultation with their doctor and with their family.

And the reason for that is because even though it has the potential of curing the patient, keeping the leukemia away, forever, it comes with it enormous risks and risks even of death, around 15 or 20%, sometimes more of patients who undergo a bone marrow stem cell transplant will actually tragically die from complications of the bone marrow transplant. One out of five; that's a huge number, obviously.

And then there will be other patients who have toxicities. They'll have risks of infections cause of a weakened immune system or risk that the new cells, which we can talk about, could attack the, the patient – we call that graft-versus-host disease – or risk that the transplant itself could cause toxicity to the organs, and a risk that some of these complications could be long term, and there's also a risk that the disease could come back.

But that said, in some of our patients, and I would say more and more as we're getting better and better at it, this can be a potential cure for our patients where the disease

never comes back and some patients they can actually have, over time go back to a good quality of life where they just live their lives without this disease.

So that is the hope. And the hope is that all of our patients would do well. But the reason that we don't recommend transplant for everybody is because of the risk of toxicities and complications, and so it's really a process to decide that this is the right thing for a patient.

And I should have started also by saying, "Why do we even, do a transplant? What's so special about it? What's different about that than just chemo? Why don't we just give more chemo or something?" So, the problem with secondary AML, as I mentioned, is that it can be unusually resistant to chemo, and so we want to be able to give something different.

There's been a lot of buzz in recent years about what we call immunotherapy, right, and that's sort of leveraging the power of an immune system with immune cells able, to target and kill cancer cells. Fundamentally, a bone marrow transplant is actually a form of immunotherapy. Stem cell transplant sort of synonyms for one another; bone marrow or stem cell transplant. It's a form of immunotherapy because what we do is, we give some more chemo to sort of, you know, it does wipe out additional leukemia cells.

But the main reason we give chemo for a bone marrow transplant or stem cell transplant is really to knock down the patient's own immune system and really to wipe it out and allow the patient to accept cells from a donor that has to be ideally sort of matched at an immune level. We call this HLA typing. And those new cells they're sort of dripped in and they go from the blood into the bone marrow. And then over the course of a month, they make a whole blood and bone marrow system for the patient including new immune cells. And those new immune cells, as they sort of wake up and see their new environment, if they see leukemia cells, cancer cells, they

see those and they say, "This doesn't look like me. It's not the body I grew up in. This is foreign. I'm going to kill that cell."

And so, the idea is that this new immune system kills off any remaining leukemia cells, and we call it the graft-versus-leukemia effect. But the problem is that those cells might not just see just the leukemia cells. Very, often they also see, of course, the rest of the patient's body as foreign 'cause it wasn't the body they grew up in. And so that's called graft-versus-host disease when those new immune cells attack the body, and they could cause skin rashes, they could cause liver problems. And so that's why transplant is this whole process and there are all these sophisticated approaches to try to balance and try to keep the what we call the graft-versus-leukemia effect but minimize the graft-versus-host disease.

**Lizette:** Yeah. Now, we're talking about chemotherapy, we're talking about transplant. Is there any path for CAR T-cell therapy for secondary AML folks?

**Dr. Goldberg:** Great question. So, CAR T-cells this is another form of immunotherapy that is incredibly exciting. CAR stands for chimeric antigen receptor. And this is, I would say, most well developed to target acute lymphoblastic leukemia or ALL. So, this therapy, CAR T-cells what happens is that we're able to take immune cells, T-cells, out of the patient and take them back to the laboratory and actually then genetically modify them. So, we introduce some new DNA that causes those T-cells to put on your cell surface a new protein they didn't have before, that is we call it CAR, like chimeric antigen receptor. And so, outside the cell could see a certain target. For example, an ALL could see a target that's called CD19. And then the inner portion of that on the inside of the cell basically tells the immune cell, "Hey, this is something you should kill and fight."

And so the idea is that now you genetically modify, you know, you have these really targeted killer cells that are designed to target specific cells that have certain proteins and then kill them off. And so if you have a good target, so an ALL is a really good

target, the CD19, which is on the surface of the ALL leukemia cells, at least the B-cell ALLs, and it's also on the surface of some B-cells, of course, in general, part of the immune system. But you can live without your B-cells. You can get infusions of antibodies. And so, it's a good target because you can give the cells to the patients, and it has side effects as well, but you can do that because there's a good target.

AML is more challenging because the targets on the cell surface for AML cells look a lot like the targets on normal stem cells. So, if we gave a target like CD34 protein, we're also going to wipe out the normal bone marrow. So, it's much harder, I would say, to do CAR T-cell therapy for AML. But that said, there's a lot of research and some really innovative work that's being done in this area. So, I say it's not yet prime time, but there are some early stage clinical trials. But it's not as developed as in ALL.

**Lizette:** Sure. And I just want to echo that we feel the same way here at LLS, that we're so excited that there are new therapies available for AML after decades of just the traditional 7+3, as you said. We have our Beat AML Master Trial which really goes into different like arms of different treatments that goes into more, you know, that individualized medicine approach it's a really exciting time right now just going from, you know, the traditional, to having more choices and treatment options that patients can really talk to their doctors about other treatments that actually may have less side effects.

**Dr. Goldberg:** Right, right. I should talk about that actually because one of the new treatments that we really should mention, which I think has kind of revolutionized the way that we treat particularly older patients with AML, in general, but also secondary AML, and that's this drug called venetoclax. So, this drug venetoclax is actually a pill and it's been studied in other cancers. And it's interesting. The way that it works basically is that it helps to remind the cells that they're cancer cells. And it basically helps to trigger a process called apoptosis or programmed cell death.

Cancer cells shouldn't develop into cancer because, they're these programs that we've evolved in all of our cells to remind a cell, hey, if you're dividing a certain way and you're not responding to signals, you should kill yourself off. You might be a cancer cell. The problem is that cancer cells, unfortunately, develop these mechanisms to resist those signals that should cause them to undergo this apoptosis.

So venetoclax, it reminds cells to undergo apoptosis. It's a pill. It works really well on its own in another leukemia called CLL. Not so well on its own in AML. It was studied and pretty low response rates, modest at best. But then it was, you know, some laboratory work suggested it may work better in combination. And so, it's now being used and is now FDA approved to be given in combination with another drug called azacitidine, and that's a sort of gentler chemotherapy, some people would even not classify as a chemotherapy really. It's a hypomethylating agent. And what does that mean? It kind of affects the way that the cells turn genes on and off.

And so, this azacitidine given seven days in a row plus the venetoclax pill – azacitidine could be given either by vein or under the skin, the venetoclax pill is continued for the month – this could be given even outpatient. So, this one's sort of a real revolution for us. You know, first of all, we always would think of effective therapy for leukemia as only being able to be given in the hospital, even the Vyxeos really, of course, in the hospital. This is now we're talking about an outpatient therapy 7 days in a row of azacitidine, 20 days in a row of venetoclax.

And so given outpatient, we thought well maybe it can't be as effective. Well it turns out it's actually remarkably effective. close to 70% of patients seem to have complete remissions with this type of treatment. And so, which is pretty remarkable. And even in secondary AML, this was now looked at in our recent study, 67% of patients achieving complete remissions. So, this is pretty impressive.

What are the drawbacks of this? Well, first of all, there's still some risk of low blood cell counts. It knocks down the immune system like before the good cells come back.

But also, unlike the sort of Vyxeos and the older chemotherapy and also transplant where there's sort of specific time limit interventions that they could then stop and then you hope the leukemia stays away. The azacitidine plus venetoclax is a therapy that's really continued indefinitely, or at least that's how it was studied. So, it's given the azacitidine once a month for the first week basically one week on and three weeks off; one week on, three weeks off in theory sort of indefinitely as long as the patient responds. And the venetoclax is a pill that the patients could take continuously.

Now some patients can achieve, as I said, most patients actually, at the beginning, can achieve these remissions. And in some patients, these remissions can last for several years, but we do worry still that even with secondary AML, the remissions may not last forever even with this. So we are starting to look at can we use this potentially less toxic but also very effective treatment to also get some of our patients maybe who might be older to a stem cell transplant that could potentially be curative? And so, we're looking at that and presenting some of that at the annual meeting in ASH and coming up this year.

**Lizette:** That is exciting. And, you know, the more treatment options for our patients the better.

**Dr. Goldberg:** Absolutely.

**Lizette:** And, you know, definitely getting the word out so our patients can start asking their physicians and their treatment teams about different options. And I know that it's probably very exciting for you to be able to present patients with different treatment options at this point.

And I know that we have, of course, in The Leukemia & Lymphoma Society we do serve patients with MPNs, myeloproliferative neoplasms, and MDS, myelodysplastic syndromes. And our patients with MPNs and MDS, they ask us all the time, is there any way that they can stop a progression to a secondary AML? Is that something that's in clinical trials right now, something that anyone is studying?

**Dr. Goldberg:** That's a great question, and we get this question all the time for sure cause I also see patients with MPNs, myeloproliferative neoplasms, and MDS, myelodysplastic syndromes, as well as patients with AML. But my MPN/MDS patients exactly ask that exact question. They come in, they say, "You're telling me that I have this risk over time progressing to leukemia. What can I do to prevent this from happening?"

And I would say that right now we do not have treatments that we know of that can definitively prevent that from happening at least in MPNs. In, MDS I would say we have some treatments that, could potentially delay the progression to leukemia. In high risk MDS, it is certainly reasonable to treat patient with azacitidine. For example, that's been shown to have a benefit in helping patients live longer. But there's, nothing really particularly for MPN patients that can fundamentally alter that possibility. But I would say that for the most part, the good thing is that possibility for MPN patients is low.

So, most patients like with polycythemia vera, for example, or essential thrombocythemia are going to live their whole lives and not have leukemia. Even patients with myelofibrosis, the vast majority of them will not progress to leukemia, but there will be some percent, 15%, you know, that will. And so, I think that the important thing is really just to continue following up, with your doctor and taking this one step at a time and not living, I would say, your life in fear basically. And as long as you're being monitored, then your doctor will let you know if there are any signs that blood counts, for example, look off and then he'll say, "Hey, I want to check your blood counts a little more frequently. Let's keep an eye on things." Or "Maybe I want to do a bone marrow biopsy to assess to see if there's been a progression to leukemia." But you're right, we need better studies and better clinical trials to try to prevent that from happening.

I will say that there's a lot of research going on in this area. You know, of course, Ross Levine, Raajit Rampal, one of my colleagues, Kamal Menghrajani, they're all

studying what are the basic mechanisms, that lead to the progression from a lower grade kind of chronic blood cancer to a more aggressive blood cancer? And there's been a lot of advances, but we still need to do better about translating that into therapies.

**Lizette:** Right, and not everybody is going to advance to-

**Dr. Goldberg:** Totally.

**Lizette:** -AML or acute leukemia.

**Dr. Goldberg:** Most patients will not.

**Lizette:** Right, right. Yeah, it's just interesting because, you're getting those questions, we're getting those questions also. Yeah.

**Dr. Goldberg:** Yeah, absolutely. Absolutely.

**Edith:** Dr. Goldberg, what are some long-term and late effects of treatment for secondary acute myeloid leukemia?

**Dr. Goldberg:** Yeah, good question. I would say that the effects of treatment, of course, depend upon the treatment that we choose. So long-term effects are important, but I also think about the short-term effects, and we talked about some of them in terms of the risk of low blood cell counts, the risk of infections, the need for transfusions.

Longer term, Vyxeos as well as, that whole class of chemotherapies can affect the organs in particular, there's a risk of the heart function being impaired. It's a low risk, but we always make sure that a patient's heart is healthy enough to tolerate that treatment.

The long-term effects of transplant can be significant. As I mentioned, patients can have what we call graft-versus-host disease. And those effects could be chronic whether it's, diarrhea or skin rashes, joint pains. Hopefully not and, hopefully, if the



patient is being very carefully followed and they let their doctors know about any symptom that any graft-versus-host disease could be addressed before it got to be, you know, really life-altering for the patient. But there definitely are a subset of patients who will have long-term effects for sure from graft-versus-host disease with a stem cell transplant.

**Edith:** Thank you. So, some patients may hold back information with how they are feeling when talking to their healthcare team thinking that their doctor or nurse doesn't have the time to listen to them. How important is it for patients to have an open communication with their healthcare team?

**Dr. Goldberg:** So important. I cannot stress enough how important that is. I totally agree. Some patients say, "I don't want to bother my doctor. You know, maybe I'll just Google this." That's not a good idea. They may find the LLS Society, in which case that would be great, you know, so they find the LLS, but even then, we want them to be in touch with us, right, because who knows what they're looking at or anyone is looking at online. And the patients that are not in touch with me, that I worry about the most because then I don't know what's going on with them. And then maybe they're struggling with the symptoms, maybe a fever. And then by the time they come in, maybe they're really sick. So, I would say always err on the side of talking to your doctor and for sure. It's never a bother to hear from our patients. It's actually our job. It's what we do. And there's a whole team of us that are here to listen and to give the best answer we can. And so just, always call. It's so important cause also, we can intervene earlier and maybe the patient might not wind up as sick if we hear about things early.

**Edith:** Right. And what are some common questions you hear from patients and their families when told they have secondary AML?

**Dr. Goldberg:** Yeah, so many questions. You know, I think one of the first questions is sort of, "Why did I get this? Why, me? Why did this happen?" And in secondary

AML, we can at least say, “Well, you know, by definition, you had either a previous blood cancer or previous treatment, but why did you have leukemia develop from that previous low-grade blood cancer or that previous and other people don’t?” And the answer is usually we don’t know why an individual patient, that patient happened to be the person who progressed to leukemia. And we’re honest about that.

The other question we often get is, “Does, is this going to run in my family? Are my kids going to get this?” And I would say reassuringly most of the time the answer is no. Almost overwhelmingly the answer is no. It’s very rare, particularly for an older adult. It would be extraordinarily rare for there to be any hereditary risk of these types of leukemia.

Now there are very, rare syndromes where there’s a risk of leukemias, one is called Li-Fraumeni syndrome, for example. And more often those are somewhat younger patients who come to attention, but in general the risk of this running in the family would be very, very low.

Other questions that I get, I should talk about supplements for a second.

**Alicia:** Oh yes, that’s another one.

**Dr. Goldberg:** People often say, “Oh man, oh gosh.” Yeah, so they say, “I found this supplement, someone in my family tells me this is going to cure my disease.” I always sit down I try to spend time and we talk about it. What I say is that, if there was ever evidence that a particular supplement was truly effective at curing this disease or even having any kind of good impact, I would be the first to recommend it for sure, 100%.

But the challenges that, you know, these supplements they’re not really regulated by the Food & Drug Administration. They don’t go through the same process that’s so rigorous to get a drug approved and many of them, maybe they might not be harmful, but they could even be harmful. What I worry about is those patients who may be taking supplements but then say, “Oh, it’s not a medication. I’m not going to tell my

doctor.” And some of those supplements can affect the liver and particularly in combination with medications that we’re giving. So, I think the main thing, the message there would be to always tell your doctor whatever you’re taking and just have an open communication with your doctor about everything. And doctors also have an open mind.

You know, we have a what we call an integrated medicine service here at Sloan Kettering, so if patients have more questions about these types of, complementary alternative approaches, I definitely refer them to that service and refer them to, you know, websites with a lot of evidence-based information like if you Google about herbs, you’ll find the MSK Integrative Medicine Service. But, yeah, so that’s just something that’s very important, to be open with your doctor about.

Then I think the big picture is, I guess the last question is really sort of, you know, what does the future look like, right? People always ask, Am, I going to die of this disease? And what can I do to prevent that from happening?” And I would say that we don’t know in an individual patient. We’re often asked, of course, we cannot predict the future, but we do have some sense of whether a patient’s disease is likely to respond or less likely to respond, and that factors into the treatments we recommend.

The main thing is just to be in touch with your doctor and this is going to be a, you know, it’s going to be a one-day-at-a-time kind of a marathon. Not, not a sprint. And we’ll go through this, you know, together and while, I don’t know, if a patient truly is going to be likely to be cured from the disease, you know, that would be my goal if I could from the beginning and we’ll do everything we can, you know, to try to give the patient the longest life possible and also the best quality of life possible.

**Alicia:** Thank you so much, doctor. You shared such great information. Is there anything that we haven’t covered that you think would be beneficial for our listeners to hear?

**Dr. Goldberg:** No, I think the main thing is just to have hope, right, and to seek out medical experts and have an open conversation with your doctors. And that there are so many new and exciting treatments that have been developed and are now currently being developed and it's an exciting time and, it's a very serious disease. It's true that I wish that our treatments were even better now, but they're getting there. And I'm so excited to be able to offer my patients better and better therapies all the time.

**Alicia:** We couldn't agree more. Thank you so much for joining us on this episode to discuss secondary AML and, again, for sharing such important information. And thank you also for everything that you do for patients and their families and touching on the importance of research and, you know, having that hope. So, thank you so much for speaking with us and for your podcasts.

**Dr. Goldberg:** My first one.

**Alicia:** For your first podcast you were incredible.

**Dr. Goldberg:** Thanks. I appreciate it. It's a, privilege to be with you all. And thank you all for all that you do to help, inform our patients and their families and the community about these kinds of diseases. It's so critically important, so thank you.

**Lizette:** Thank you.

**Alicia:** Dr. Goldberg, you touched on something that was so moving and relatable for me, your relationship with your grandmothers which helped to pivot you to begin the journey of becoming a doctor based on their experiences and own health challenges. My grandmother was a huge reason for why I decided to join LLS, which is why it resonated with me so much. After having been diagnosed with cancer, my grandmother would always remind me, she would say, "Alicia, choose the noble choice every time and God will do the rest." And I had seven incredible years here at LLS. And for those listening who have become like family here on this podcast, this will be my last episode as I venture out to begin a new journey.



Thanks for everything each listener has taught me and thanks to my amazing guest hosts who made this job so enjoyable each and every time you brought information to patients and their loved ones. No one could have predicted that three, almost four years ago when this podcast was created that I would be creating something that would touch people in so many ways. And I am blessed to know that so many people are benefiting from it.

So, again, thanks for listening and thanks for all of your time and attention throughout the years.

And for those listening who would like to learn more about secondary AML by viewing our past programs, please visit [www.lls.org/program](http://www.lls.org/program). Thanks so much for listening.