

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Treating Acute Myeloid Leukemia (AML)'

Description:

There have been few advances in treatment for AML in 40 years. Why is acute myeloid leukemia (AML) so difficult to treat? What is the current treatment for AML? How is The Leukemia & Lymphoma Society (LLS) striving to change that? How are targeted therapies being used for patients? Is immediate treatment for patients necessary for all AML patients? How does a patient's ethnic background play a role in finding a matching bone marrow donor?

Join Alicia and Lizette as they address these questions and more with Dr. Martha Arellano from Winship Cancer Institute of Emory University in Atlanta, Georgia. On this episode, Dr. Arellano addresses current treatment and treatment advances for AML, including stem cell transplantation and cellular therapy. She also explains the goal and impact of the Beat AML Master Trial, a groundbreaking collaborative and targeted clinical trial for patients with AML.

Transcript:

Alicia: Welcome to The Bloodline with LLS. I am Alicia.

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

Alicia: Today, we will be speaking again with Dr. Martha Arellano, Associate Professor of Hematology and Oncology and Program Director of the Hematology and Medical Oncology Fellowship Program at the Winship Cancer Institute of Emory University in Atlanta, Georgia. Thank you so much for joining us again, Dr. Arellano.

Dr. Arellano: Thank you so much for having me.

Alicia: On a previous episode with you, we spoke about diagnosis, symptoms, possible risk factors for AML. So, for those listening, we encourage you to listen to that episode as well for more about that information and for a more understanding of the basis of AML, but on this episode, we will be jumping into the topic of treatment. Before we jump into treatment, what is AML for the person listening that didn't get a chance to listen to that first episode with you?

Dr. Arellano: Yeah; certainly. So, AML is a blood cancer. It starts in the bone marrow. The bone marrow stem cells which are normally invisible to the eye, even under the microscope, can acquire mutations in their DNA and, if our body is not able to get rid of those mutated or damaged cells, then these cells can continue to grow out of control. And normally, we shouldn't be able to see stem cells, even under the microscope, in the bone marrow or those in the blood and, in leukemia and AML, these cells grow so quickly that they fill the bone marrow space and then they start to spill into the blood. And the definition of AML is that those leukemia cells, which we call leukemia blasts, are 20% or more of all the cells in the bone marrow or the blood. So, at the same time that those leukemia blasts are overcrowding the marrow, they also cause what looks like a bone marrow failure-type of syndrome where the marrow is not working, well and it is not making enough of those normal blood cells that are needed for us to be able to fight infection and to be able to not bleed and to have the adequate energy with the adequate level of hemoglobin. It is basically a blood cancer that starts in the bone marrow.

Alicia: When it comes to AML, we know that, despite advances in treating other blood cancers, the standard of care for AML patients hasn't changed in the last 40 years. What's the cause for that or the reason for that?

Dr. Arellano: It is a rare disease and even though there has been a lot of research done, I think in the past few years, there has been a, tremendous increase in effort in investigating the causes of AML and the make-up of all these genetic mutations that happen in those leukemia cells that make it so difficult to treat. And so, even though the treatment, for many years the standard had been the same, there are actually some newer, more exciting options today and a lot of research that is still ongoing.

Alicia: Right. And, like you said, the effort is there. LLS has been on the forefront of the battle against AML so I think it is important to understand that because of how complex it is, that's what preventing us from figuring it out, I guess you could say, and getting down to.

Dr. Arellano: Correct.

Alicia: Yeah...and getting down to more and more of a firm resolution for having treating patients and cure them.

Dr. Arellano: Yes; exactly. An AML cell can have so many mutations that it's hard to figure out which mutation is the driver of the disease so that if we target that mutation, do we get rid of the disease? And then, there is some data that shows that the different blasts in the same patient with the same AML, different blasts can have different mutations. So, you may be targeting one thing that you think is the driver, but then months or years later, new mutations may pop up and cause that leukemia to relapse or to progress.

Lizette: So, as Alicia mentioned, there's a lot of new things coming up in AML. There wasn't a lot of things before, but now, interestingly enough, there's new approvals, for AML therapy. Can you talk about some of those?

Dr. Arellano: Sure. historically it was one size fits all, right, induction chemo for everybody whether they were likely to benefit or not, and the only other option was, palliative care or blood transfusions, antibiotics and hospice. And so, here in the past two years, we have had 8 approvals in new drugs approved for AML and that's just in—you know, no drugs have been approved for many, many years. And these drugs are, I think the discovery was, was sparked by the discovery of all these gene mutations and we are going to see more approvals of these drugs as we discover more genetic pathways that are affected and also use that information. For a long time, the molecular or gene mutation information that we could gather was only used to predict prognosis and, now, that is actually translated into actual targeted treatments. So, a very exciting time in the treatment of AML. There are also immunotherapies, treatments that aim to train the immune system to target the leukemia cells within the patient's body.

Alicia: That is very encouraging for the AML patient who, like I said, 40 years of no advancement and then to hear there would be some progress. I mean this is something that people are living with and kind of always having their ear to the cement about what was happening so that's very encouraging to hear.

Dr. Arellano: Yeah; yeah. There's a patient that I was seeing today who was considering the various treatments and I was just telling them, you know, there's a brand-new treatment that I think will likely become the standard of care for those patients who are not likely to, benefit from induction treatment. So, there's a drug called venetoclax, which is a pill. It's already in use, it has been used for some time for chronic lymphocytic leukemia and multiple myeloma, but now it's been recently

approved for patients that are older that are newly diagnosed with AML and their remissions are in the range of 70% in combination with another group of drugs that are being used. They are called hypomethylating agents and so that has really been a break through. There are other medications, there are two drugs, that inhibit a mutation called SLIT3 or FLT 3. One of them is called midostaurin, which was approved to be used in combination with induction chemotherapy in those patients that have AML with a FLT 3, type of mutation. And then more recently, there's another drug called gilteritinib, which is another FLT3 inhibitor also approved. That one is approved for relapsed or refractory AML. In terms of other genes, there are 2 genes. One is called IDH1. The other one is called IDH2. These genes, I was talking with one of my patients about this and I was saying, "remember the Krebs cycle in biology class and she said, "oh my gosh, yes. These genes are involved in the Krebs cycle and when they are mutated, they tend to be drivers of AML. So, about 10 to 12% of patients have mutations in either IDH1 or IDH2. And so, now we have an IDH1 inhibitor that's FDA-approved and an IDH2 inhibitor as well. And then there's an antibody treatment that was previously FDA approved and then there was some safety concerns with it; and it went off the market for some years and it was just brought back. It's called gemtuzumab ozogamicin. It's an antibody that targets something that's called CD33, which is a marker on most AML cells, pretty much all of them, and so, you know, there has never been so many new drugs.

Alicia & Lizette: Absolutely.

Lizette: And I think what's exciting, too, what you were saying, that a lot of this is coming about because we are finding new mutations, and as we are testing for these, we're realizing that we could do something more in the personalized medicine; meaning that, not everybody is getting 7 plus 3 so...

Dr. Arellano: Exactly.

Lizette: it's you know, going to be tailored to the type of AML that you have so you have, I think, a better chance of the therapy working if you know that the therapy has worked for your type of mutation. I know, here at LLS, we are doing The Beat AML trial and really that's the core of what we are trying to do which is really that individualized medicine, where a person is given something that, hopefully, will treat their disease, not just AML in general.

Dr. Arellano: Exactly; so, I was going to talk about that. The Beat, B-E-A-T, not B-E-E-T.

Alicia: The verb.

Dr. Arellano: Exactly. So, Beat AML—it's a very large study. We are one of the sites for Beat AML at Emory. And patients consent and provide a bone marrow aspirate which is analyzed, for microscopic analysis, chromosomes and the genetic mutational analysis. Then we get that information back and, based on the mutations that the leukemia cells have, the patient is allocated to a specific treatment. And there are many sub-studies. There is an IDH1 inhibitor sub-study, an IDH2 inhibitor sub-study. There is a p53 sub-study. P53 is a gene; that one is mutated. It predicts a very poor prognosis and there is a drug that we think targets p53 and we've seen a few remissions using that drug so it is very promising. And then for those patients, if there are patients that don't have any targets or they have genes for which there isn't a drug, a targeted drug, so then those patients go on to a standard type of trial. So, there is one thing that patients will ask me is "will I be getting a placebo?" And I tell them there is no placebo for this. Everybody will get treatment. Everybody will get at least what is considered standard or a hypomethylating agent plus a targeted treatment, so that is a very exciting trial.

Alicia: What is awesome about this trial is that, you know, the collaboration continues to expand into to include multiple academic institutions so a lot of people are able to have access to this if they are in those areas, of course, but I think it's something great for AML patients, like you were mentioning.

Dr. Arellano: Yeah; absolutely.

Dr. Arellano: For many patients with AML, a clinical trial is the best option.

Alicia: Right. And for those listening who would like more information about this trial, you can visit www.lls.org/beataml, B-E-A-T AML.

Lizette: I think what's also important and I think it is true, please, doctor, tell me that some of these newer medications, don't they have less side effects for patients?

Dr. Arellano: Exactly. The BEAT AML trial is for patients older than 60 because these are the patients that tend to have a lot of other medical problems that would put them at risk for side effects from the strong induction-type of treatment, although there is an induction arm for Beat AML, by the way. And so, these drugs are by design supposed to be better tolerated for these older patients. I've said it, but I haven't said what are. The hypomethylating agents—there are 2. They are called azacytidine and decitabine. They are FDA-approved in this country for MDS, but they're pretty broadly used for patients that are older or frail or that have a lot of other medical problems and are not candidates for induction chemotherapy; so, they are used in AML. The initial clinical trials that were said these drugs for MDS, actually had AML, by the former definition of AML which was 30% blasts and somehow the new definition is 20% blasts or more. And so, those patients essentially, and there was a response rate, you know, a rate of complete remission in these patients who will, back then had MDS, but today have AML. And so, these newer agents tend to be added to the backbone of hypomethylating agents, either as azacytidine or decitabine. And they're a lot less toxic. Patients, I had a young 80-year-old who asked me, "will I lose my hair" and it's like "not that I really care, but I am just curious, will I lose my hair?" Patients are not losing their hair after getting these hypomethylating agents.

Alicia: Wow!

Dr. Arellano: Yeah, so they are less toxic.

Lizette: That's good to know. That's very important.

Lizette: I think one of the other things that, I think is a breakthrough to know is that we always thought of AML as something that had to be treated right away. You're diagnosed and you have to be treated right away. Here, we are finding that we can successfully, hold off to get the actual test results to see if a patient has any of these markers that we can target, before starting treatment so we can actually specialize that treatment for that person. So, I think that's a new concept. I know it's a new concept for me for AML.

Dr. Arellano: You know, yeah; that's a very good point. I'm glad you brought that up because a lot of the patients that I see that are referred had already had one cycle of something whether it's a hypomethylating therapy or something else. , and I think if the patient is not in an emergency situation where the white count is through the

roof and, you know, you really don't need to do something right that second, there is time to get that diagnostic information to make sure that we make the right decision and also to involve the patients in a clinical trial. Some of the patients that I have seen with recently diagnosed AML come in after they've had one cycle of either decitabine or azacitidine, and so now they don't qualify to go in the clinical trial. And we know that those drugs will not put someone into remission after just one cycle so...

Alicia: And sometimes a stem cell transplant is recommended for an AML patient. The two types being allogeneic and autologous stem cell transplant. When is it determined which one will be used for the patient or for a patient?

Dr. Arellano: Yeah. So, for the majority of patients who we think are candidates for a stem cell transplant, they will be a candidate or we will recommend an allogeneic or a donor transplant. There is only one type of AML where autologous or a transplant from a patient's own cells can work and that is in patients with acute promyelocytic leukemia which is a subset of AML; a type of AML that is treated differently. In those patients, an autologous transplant, after the disease recurs and they are back in remission, could help, but for the vast majority of AML patients and for all of MDS patients, we will recommend the transplant is going to be an allogeneic transplant.

Alicia: Okay.

Dr. Arellano: Autologous transplants are mostly used in the space of multiple myeloma and lymphomas, certain lymphomas.

Lizette: And you mentioned a new treatment that was just also newly approved for patients. I believe that started with myelodysplastic syndrome, and then were diagnosed with subsequent AML.

Dr. Arellano: Yeah; so that is called Vyxeos®, and that is a liposomal combination. It's like a 7+3 that's put into a liposome in a specific ratio and if that lipid, white cell or that liquid globule, the drug—the two drugs maintain that ratio. And there was a clinical trial that compared Vyxeos® with 7+3 induction in these patients and it was better at its end point so it became FDA approved. And so that is what we would use now in somebody that has AML after MDS, or AML with MDS-related changes.

Lizette: And that's great because those patients were higher risk patients, correct?

Dr. Arellano: Right; right; yeah. And those patients are still candidates for stem cell transplantation. One question that patients will ask me is if I am a candidate for transplant, when can I get it and why can't I get it upfront?

Lizette: Right.

Dr. Arellano: So, and so stem cell transplantation has the biggest success with, patients that are in remission. So, we know that when someone is in remission—so remission means that we cleaned out the bone marrow—all the bad cells—and now the bone marrow is functioning and making good cells. but even patients who are in remission still have microscopic disease that is not—that we are not able to detect by the best tests that we have and that's why the leukemia comes back. And so, immunotherapy and allogeneic transplantation is one of the longest living immunotherapies. It works best when there is very little disease there. And so, if someone comes in with a white count of 100,000 with AML, we are not going to do a transplant right off the bat because it isn't going to work. So, you get all the toxicity and none of the benefits. So, we want to get the patient in the best condition, you know; in remission and with as few side effects from the chemotherapy as possible. That's the other thing that patients have to be in very good health before going through a donor or transplant.

Alicia: I was reading a story of a patient who was diagnosed with AML and, she had progressed so rapidly and they had caught it so late that the doctors had basically told her family to come in and say their good-byes. Well, what ended up happening was she decided to go on a clinical trial and she just said, "you know, since the odds are looking so grim anyway, I might as well" and it ended up working for her. And, she started to feel better to the point where the doctors introduced the possibility of a stem cell transplant. And, what was interesting is was she had many siblings and the siblings matched each other, but they didn't match her.

Dr. Arellano: Oh wow!

Alicia: Yeah; yeah; so, she basically shed light on the fact that being of mixed ethnic background, she spoke about her, you know, there's many Americans of European descent that find a match, but only about 19% of African-Americans do, according to a recent New England Journal of Medicine study. So, she stressed the importance of what it means be a donor and be that need for another person because of how low the

numbers are for those of mixed ethnic or racial background that are under-represented in the registry.

Dr. Arellano: Yeah, exactly. That an amazing story. And, I've seen that in my clinic as well. You know, someone that came for a second opinion, and I decided to try a treatment on them, and they ended up doing well. And yeah, so there's a critical need for bone marrow or stem cell donors in minority races, black, Hispanic, American-Indian, and mixed races because the way that the HLA typing works, the less mixed you are the more likely it is that you will have a donor. And, so my patients will often say, you know, should I start a bone marrow drive just for me or should my cousins come and get tested just for me? And I generally tell them to go ahead and, you know, have that bone marrow drive and have everybody get tested, but to get into the registry so that even if they can't help you, they can help someone else.

Alicia: Right.

Dr. Arellano: I am in the registry, but I have never been called.

Lizette: Me neither.

Dr. Arellano: I'll donate if I get called.

Alicia: Right; right. Not only are mixed ethnic or racial backgrounds under-represented in the registry, but they also have greater diversity in their tissue types as well, right?

Dr. Arellano: Right; exactly, yeah. So, you know, I say if I ever needed a donor, there would be one because I am just so mixed. My father was from Ecuador; my mother is from Colombia; my grandfather was from Vietnam.

Alicia: Wow! But you know what? What was interesting is the physicians of this patient that I was speaking about, they told her to pursue another route and she ended up doing the umbilical cord blood.

Lizette: Cord blood.

Alicia: Yeah; and that is what ended up saving her life and now she is a healthy, long-term transplant survivor and mother of two.

Dr. Arellano: Wow! There are a lot of advances in the stem cell transplantation and cellular therapy fields, as well. There are transplants that are half-matches when we can't find—so the best donor, right, would be a sibling that has identical HLA typing. Then the next best would be an unrelated donor that is identical, but when we can't find the best-case scenario, then we have half-matches or haploidentical transplants where children or parents are matched together. And then, cord blood transplant is something that is relatively, new, but also an option for those patients who would not otherwise have a donor.

Alicia: And for those listening who would like information about stem cell transplant or to speak with one of our information specialists, you can give them a call at 1-800-955-4572 anytime Monday to Friday, 9 a.m. to 9 p.m.

Lizette: Eastern time.

Alicia: Eastern time. That's important; that's important.

Lizette: I just wanted to, ask you about CAR T-cell therapy for AML. So, everybody is hearing about CAR T-cell therapy. Right now, it's approved for two indications within the blood cancer space and a lot of people are really asking, "is CAR T-cell therapy something that is going to be a future treatment for AML?"

Dr. Arellano: So, it is, yeah, like you said, it is definitely a—it's here now for ALL and certain type of lymphomas, but it is investigational for AML. So, it is possible that it will be a treatment option someday.

Lizette: This is great. Which is just another treatment option. Can you tell people what it is just because we do have some people that, don't know what CAR T means at this point?

Dr. Arellano: So, CAR T cells, Chimeric Antigen Receptor T-cells, they are engineered T-cells where we collect the cancer cells, the leukemia cells, from the patient and then their own T-cells are engineered to recognize the cancer cells; and then we infuse them back into the patient and their job is to kill the leukemia that they were trained to

recognize. And so, one of my patients that, was treated with CAR T-cells for ALL said, “how are my little soldiers doing” because when I described it to her, I said that they were like little soldiers that were trained to recognize your leukemic blasts that we can’t see and they are going to kill them. Some people call them smart bombs. I don’t like to use the violent words to describe them, but that was the best way that I could describe them.

Alicia: We were talking with a doctor who said that he was talking to his patient and he was seeing how interesting it is how patients, kind of, rationalize their disease and one of the patients said, “I consider it like a rottweiler and a chihuahua”. And the doctor was like, “how did you draw that conclusion”? So, whatever makes sense; whatever makes sense to the patient.

Dr. Arellano: Exactly, yeah. So, my patient who had CAR T-cells for ALL. We try not to give steroids to those patients during that treatment because the steroids can kill the T-cells. That’s why steroids are part of the treatment for certain types of leukemia. And so, she got pretty sick and I ended up giving her steroids and she said—and this was days later—I thought that she had forgotten that whole little soldier conversation, but she said, “how are my little soldiers? Did you kill them all?”

Alicia: Awe! Awe!

Dr. Arellano: No; I think they are going to be okay.

Alicia: It’s so great to have that type of relationship with your doctor because you are already going through something that is so life changing and so traumatizing so when you are able to have that connection with somebody who is there to, I mean, save your life, it’s one where you want to be able to have that type of relationship and feel comfortable knowing that the person that’s alongside you, you know, on this journey is one you can trust.

Dr. Arellano: Yeah; absolutely.

Lizette: And understand because a lot of times, you know, you go in—I know I go in, and sometimes the doctor will say something, and I didn’t understand, but I don’t want to say, “I’m sorry, I didn’t understand that, you know, could you say it a little bit different?” But just to make it understandable, I think, is really a big deal. I think that

just that conversation with your doctor. We have so many people calling our Information Resource Center and asking us questions that, you know, we do kind of say, “what did your doctor say about your personal, situation?” And they say, “well, I didn’t really ask my doctor. I had 15 minutes with my doctor and they are telling me about my blood counts and they’re telling me it’s really good” so really, you know, that’s not a place to talk about any quality of life issues or, you know, how this is working for me in this way; and we really encourage people to let them know that they can actually ask their doctor, especially to make it understandable. And I think that’s a great way of putting it because CAR T, when you actually look through the whole process—can be a little bit confusing, but how cool is it, you know, to understand a process that let’s, you know, your own immune system is actually killing something that is bad that it didn’t recognize before that it’s bad. Now it does. I think it is, you know, a really cool concept and to actually understand it that way, that’s great.

Dr. Arellano: There are many patients that, you know, I feel like all of you came for a second opinion and I wasn’t able to help you in any way because I don’t have, you know, a better treatment to offer. and oftentimes, they’ll say, “you actually did help because you gave more information than I’ve gotten in weeks or months”. and one patient—so I draw a lot of pictures. I draw a little picture of the bone and the cells, and explain how the bone marrow works, and how the blood works, and so—and I do it all—I tell the Fellows if you are systematic and always do it the same way, you won’t forget, you know. Plus, you get more efficient at doing it and not using a lot of time. But I was going through my spiel with some of my patients and she said, “you’re a school teacher, aren’t you?” It turns out, I used to be a pre-school teacher...

Lizette: Oh!

Dr. Arellano: ...in a previous life. But I just tell her I know what it’s like when you go to the doctor and they’re using so many technical words and you don’t want to feel like you’re stupid by asking something or interrupting, so I tell them, “feel free. Ask me anything. You know, cut me off if you need to, if you don’t understand.”

Alicia: And it’s so beautiful to know that the doctor you are seeing, doesn’t mind spending more time on something. I mean, for me personally, when I go to the doctor and I am rushed along, I feel like it was a complete waste of time and I get upset. And I am like, I don’t think he heard me. And when I go to a doctor who will explain

things multiple times or, like you said, draw a picture or just take the time, that makes all the difference for somebody who is already going through such a rough time.

Dr. Arellano: Yeah; that is a very stressful time. One thing that's important, while you are saying that, is to bring someone else to the consultation because the two ears aren't going to hear everything.

Alicia: Hmm; hmm; yes.

Dr. Arellano: Especially if it is the first time that you are going for a new patient visit or a consultation where you are going to get a lot of information, I think it is good to have another set of ears.

Alicia: Absolutely

Lizette: Most people say that after they hear the word cancer, everything after that is

Dr. Arellano: ...a blur.

Lizette: ...too much. Yeah; yeah.

Alicia: That's so true; And that's really what Lizette and I, on this podcast, that's really what we try to, create for people is when we talk to HCPs, we want them to know that it should be conversational, that they shouldn't approach a doctor's office or a doctor with fear, but to really feel empowered when it comes to their health and their diagnosis. And the information is out there, you know. Having access is everything. So, we really want to be that source of information for people so that they know. They know that we are here and they also know that they also have the power to approach their diagnosis boldly, as scary as it may be.

Dr. Arellano: Yeah; yeah. This is—it's wonderful that you do this; yeah!

Alicia: Yes; Dr. Arellano, is there anything that you think we didn't cover that we should cover regarding treatment?

Dr. Arellano: I think that's it. I think that's pretty much it. The younger patients do ask about fertility issues, but...

Alicia: Yeah.

Dr. Arellano: if that's a concern, children down the line, they should bring it up and there might be options.

Alicia: Absolutely; absolutely. And for those listening, who would like information about AML, Beat AML, about fertility, we encourage you to visit www.lls.org/booklets to download or order any of our free publications.

Alicia: Thank you so much for speaking with us about the treatment of AML. It's been so great chatting with you, Dr. Arellano.

Dr. Arellano: You're welcome. Thank you so much for having me. It was fun.

Lizette: Thank you!