The Bloodline with Blood Cancer United Podcast

A Podcast for Patients and Caregivers

Episode: 'Inside CAR T-Cell Therapy: How Innovation Is Changing Lives'

Description:

CAR T-cell therapy is redefining what personalized cancer treatment can look like, offering real promise for patients and families.

In this episode, we speak with Dr. Richard Maziarz and CAR T Nurse Coordinator Bashi Ratterree of Oregon Health & Science University (OHSU). Together, they explain how CAR T-cell therapy works, who may be eligible, what patients can expect during treatment and recovery, and the promising advancements shaping the future of this innovative therapy.

Transcript:

Elissa: Welcome to *The Bloodline* with Blood Cancer United. I'm Elissa.

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

Elissa: Today, we are speaking to Dr. Richard Maziarz and CAR T Nurse Coordinator Bashi Ratterree of Oregon Health & Sciences University, or OHSU, in Portland, Oregon. Dr. Maziarz is a Professor of Medicine and a Program Leader of the Cellular Therapy Program at OHSU. He has served as the principal investigator or co-investigator in over 200 clinical trials focused on CAR T-cell therapy, stem cell transplantation, and other cell therapies.

Bashi has been an oncology nurse for over 20 years and now serves in the Immune Effector Cell Therapy Program at OHSU. In this role, she is part of the care team for CAR T-cell therapy patients and helps them and their families to navigate therapy and recovery. Welcome Dr. Maziarz and Bashi.

Richard Maziarz, MD: Thanks for inviting us to participate.

Elissa: Well, thank you for being here. So, our episode today is on CAR T-cell therapy. Could you tell our listeners what that is?

Dr. Maziarz: CAR T is an abbreviation for chimeric antigen receptor T-cell therapy. Let's start with saying that the immune system has many arms. And one of the arms is the lymphocytes, and the lymphocytes are divided into multiple populations. But there's one population that is particular called T cells, and T cells are probably one of the most important immune populations to protect you from infection, from viral infection in particular, as well as cancer-forming events. We all depend on our immune cells, and we depend on our T cells. And just for interest, when you're vaccinated as a child for polio, you have long-lived immunity; and it's through your lymphocytes. And there are T cells in your body 40 years later that are still specific to protect you from that polio virus.

What this CAR T therapy is, is people have learned how to capture lymphocytes from an individual and genetically modify them to put a genetically reorganized receptor. People have figured out, and this goes back to work over 20 years ago, how to genetically reconstruct the binding site of an antibody onto the machinery that activates a T cell. So, now what you have is a chimera, going back to Greek mythology, is a fusion of multiple animals. If I remember correctly, wings of an eagle, body of a lion, and, I believe, head of a goat. But that's a chimera, and so in this way it's a product of an antibody and the T-cell molecule genetically modified and put back into healthy lymphocytes. So, those healthy lymphocytes will have its own receptor, but it will now have this fusion, this genetically reconstructed receptor that could be targeted to whatever you so choose. And what most commonly is, people are identifying molecules that are associated with a particular type of cancer, as a particular tumor, and then creating this product outside the body; and then it can be reinfused.

Now, one of the beauties is, people call this the living drug because the same lymphocytes that may be in your body to protect you 40 years later from polio virus, they may be those cells that were genetically reconstructed to express the molecule. And so now you put this drug in, but instead of having a short half-life, like a pill might have or an antibody might have, now the cell can live weeks, months, and even years. There have been studies, that have gone back to some of the earliest patients treated with CAR T who were cured by CAR T; and ten years later, people drew blood and could identify CAR T cells in their bloodstream.

So, it's the living drug, and it does take time. It's a lot of genetic manipulation. It's a product of all the research that a lot of folks have done. But what it is, is we're creating living biologic drugs. And it is, by the way, a drug. The FDA (Food & Drug Administration) has declared it a drug. It is a little different than what we think about our typical cancer drugs which are often designed to kill a cell. And so, if you give a drug that kills a cell, it can be indiscriminate. It will kill cells, and it will kill cells that may be what you're trying to target but kill other cells. So, classic chemotherapy, nausea and vomiting, diarrhea, GI (gastrointestinal) side effects because the GI tract heals quickly and grows quickly, so it's susceptible to drugs that kill all cells. CAR T is designed to kill one cell, which is the cell that you created the chimeric molecule to.

I mean I had a patient once who actually was from the Pentagon, and after these descriptions, he all of a sudden, he turned to me and says, "I got it. You guys are giving me smart bombs," because he could understand a smart bomb. He couldn't understand CAR T cell.

Elissa: Okay, so essentially, you're putting instructions into these T cells to recognize the cancer cell and attack it and leave all the healthy cells alone?

Dr. Maziarz: Well, it's not necessarily an instruction. It actually is a molecule that will directly bind the target and then once it binds, the tails are already activated. They'll do their job, which is to kill whatever it binds to.

So, it is a drug, and the cell is the drug. Now, I can't say it will only kill the cancer cell because if there's a normal cell that still expresses that molecule, it also can be depleted. But it's really important though that we're very selective in how we identify a target for when we generate a CAR T cell that the potentially on-target/off-tumor effect is only going to be killing off cells that your body doesn't necessarily need or you can live without.

Elissa: So, what blood cancers are currently eligible for CAR T-cell therapy?

Dr. Maziarz: So where it started with is certainly blood cancers. And if we start with the clinical trials that have emerged that led to successful approval by the FDA of treatments, we're going to start with lymphocytic diseases. So, we're going to have acute lymphoblastic leukemia, or ALL. We're going to have large-cell lymphoma, which is an aggressive lymphoma. We're going to have lower-grade lymphoma called follicular lymphoma. We're going to have subtypes of lymphoma called mantle cell lymphoma and now, most recently, marginal zone lymphoma.

And then we also, in the midst of that, have chronic lymphocytic leukemia, which some people would say is the same as small lymphocytic lymphoma. So, it's in a class of agents that are all in the lymphoma line. Now, in the last three years though, there's been progress at a different type of cancer, which is multiple myeloma.

Elissa: Yes.

Dr. Maziarz: And we have drugs approved to treat multiple myeloma. Now, there's a lot of exploration for CAR T in other situations. That is still experimental. Those, what I told you, is what's FDA approved and indications, standard of care. What's coming is a variety of solid cancers, as well as, and I say solid cancers, I mean we have studies that have looked at lung cancer with CAR T, breast cancer, gastric cancer, now pancreatic cancer.

Elissa: Wow.

Dr. Maziarz: And also, the extension is you can now take it to other diseases like autoimmune diseases. So, there's patients with lupus, Sjögren's disease, scleroderma, myositis, multiple sclerosis. These are all new future indications.

Elissa: That's exciting. Wow. Now I noticed that you didn't mention any myeloid malignancies, so acute myeloid leukemia, chronic myeloid leukemia. Is there a reason why CAR T-cell has not worked yet for myeloid?

Dr. Maziarz: Well, there's a lot of reasons. That's a very good pickup on your part. And so, myeloid leukemia is the CARs will work. You can target them, but at the moment the targets are going to be the same molecules that your healthy bone marrow depends on.

Elissa: Oh.

Dr. Maziarz: So, if you're using CARs to target a myeloid malignancy, you will destroy the ultimate bone marrow at the moment, the way it is now; and so, you have to plan to rescue that person with a bone marrow transplant.

Now, there's some beautiful biology that was just recognized recently explaining why myeloid leukemia has been so resistant. And it does turn out that as the CAR Ts try to kill the cell, it also creates a lot of inflammation; and a lot of inflammatory molecules, it turns out leukemia cells, AML cells have receptors for. And so, while you're trying to kill the AML, the inflammation that's associated, the AML is getting those factors and using it to revitalize themselves.

Elissa: Yeah.

Dr. Maziarz: And so, people are working very hard to work on means by which you can shut down that component of the inflammation and take advantage of the CAR T development. It is in progress.

Elissa: Okay.

Lizette: Yeah, now, are there any additional factors you need to consider to see if a patient is eligible for CAR T-cell therapy, like age, comorbidities?

Dr. Maziarz: Yeah, another great question. And when the trials were done, there were very, very specific guidelines to make it safe. And we've been doing this here at OSHU since 2000 and, I think 2015 was our first patient, but we were involved in helping develop the trials starting in 2012.

We've learned a lot in the last decade, like focused on how to make it safe because early on it was felt that if we give the treatment, we do not want to give anything to disrupt the treatment, and so people got sick. So, we had to make sure that someone had the reserve to survive and to get through being very, very sick to make it worth the while. Plus, at the time, we didn't know that we were going to cure people.

Things have changed over the past decade. When it gets to that question, though, is what have we learned. So, I'm going to say if you go back to the original trials done in lymphoma, the average age of the patient was 55, 56, 57. We're now treating patients in their 80s.

Elissa: Wow.

Dr. Maziarz: And previously, one of the studies from one of the registries that collects patients. It's one of my favorite studies to quote because when you look at patients from age 18 to age 90, divided in four different age groups, with 75 to 90 being the oldest age group, there was no difference in the degree of inflammation risk that was experienced. There's no difference in the likelihood of benefit from the treatment itself. There was more of a confusion state and sort of a neurologic toxicity we'd experience in the older patients, but the likelihood of benefit was identical.

And so, we've learned how to do this. We also have to be careful though that as we start to offer it, we understand what are the factors that predict that the CAR T is not going to work at all? And sometimes that goes into how fast the tumor's growing. Is it going to grow faster than our ability to take the time to manufacture the product? Is it going to be the fact that the disease burden is so large at the time that we may get a benefit in shrinking it; but it's a one-time therapy, once you deliver, it's going to be growing back. And honestly, when the drugs were first approved by the FDA, they were approved for the goal that they're being compared to a curative therapy. That's where the big things that's changing right now is where we're starting to think about, we're tapping diseases that we may not cure, but we may change the natural history. We may extend the survival of an individual. We may add one year, two years, three years or more by this intervention.

Maybe we don't have to cure everybody, but maybe we can even find ways that we could treat repeatedly. Again, those are all experimental questions that are being asked now that we've learned (1) how to do it, (2) how to find the right patients, and then (3) how to support people through it; and supporting people through it is really critical.

Elissa: So, once CAR T-cell therapy is determined to be a good option, what is the conversation that both of you are having with patients and caregivers; and how are you addressing them?

Dr. Maziarz: Well, let me just start briefly by saying access is a critical issue.

Elissa: Yes.

Dr. Maziarz: At OSHU, we were part of a study that actually could quantify. We looked at a Medicare database, like who gets referred. And for every 30 miles you are from a treatment center, there's a significant drop-off of patients who come to see you. And so, patients who live 200 miles away, the distance is a barrier.

Elissa: Yeah.

Dr. Maziarz: And then also, do you want to leave home? I may be leaving home and may not work. Maybe I'll just stay here. So, I think one of the first things we have to overcome is that fear of relocation, the fear of being away and that we're going to do our best to make this comfortable for the patient. We're going to try and make a community with the patient.

And then, we also have to work very closely with the referring physician. We make it very clear that you come here, we will be your doctors, we will be your nurses, we will care for you when you're here. But your main doctor is the one who's been caring for you for the last six months, twelve months, two years. We're there to help them. They're your doctor. We're, basically your consultant. It just turns out that we get pretty involved as a consultant.

Bashi Ratterree, RN, BSN: I agree. I think it can be so challenging for patients leaving home, leaving work, leaving family. Oftentimes, they're caring for people themselves, whether they're children or elderly parents and just picking up and moving to Portland; and CAR T comes in steps. So, we have the collection. They have to come for that, after the consult even. And then they have to come back for five weeks for the actual infusion portion of it, and that can be really challenging for patients to be away from everything for that long and oftentimes, live in a hotel room away from their comfort of their community and their home.

So, we do, as the whole team, definitely support them as much as we can. Our social workers are amazing. Our care coordinators, our physicians, just across the board we do everything we can for these patients. It can be such a challenging process for them.

Lizette: Sure.

Elissa: Yeah. That's a very important point because especially with the Pacific Northwest, you're really only having CAR T-cell available in Portland and Seattle. And so, we have Alaska, Montana, Idaho, all of Oregon, Northern California really having to travel a very, very long distance to be able to get that therapy. And that's a huge deal to have to leave your home for a while and your work. And so, it's great that there are support services available to try to make that therapy accessible to as many people as possible.

Dr. Maziarz: Yeah, it's important also to pick up on one thing, it's also a team effort. In the same way a patient has their team, they have their family, their friends who are helping them – whether it's locally or relocating. They have a team who we depend on a team that will provide them the ability to give them that care because for a period of time, it's often a 24-hour/7 days a week close attention to that individual just to make sure that there's a lot of investment on the patient's part to go through with. There's a lot of investment on society's part to support it, and so we have to deliver the best possible team effort to get through this window of time where there could be risk where the benefit then emerges.

Lizette: Right. And besides overcoming these barriers and the logistic questions, do you get a lot of different concerns from patients and caregivers about the therapy itself? What kind of questions do patients and caregivers have?

<u>Dr. Maziarz</u>: Well, it is a procedure. It is a therapy. It's our job to share risk and benefit. And honestly, the benefit's easy to tell somebody. "We could shrink your disease; we can get it back under control. Maybe we can put you in remission; maybe we can eradicate it." And that's easy to say, but then to be fair, they have to understand there's uncertainty and (1) it may not work, (2) the disease will give you a benefit for a short period of time and then the disease may come back. You have to emotionally prepare for that.

But there are these, what we call the adverse events of special interest. That's what the FDA called them. The AESI, the adverse events of special interest, which is this very early, very aggressive and, it can be a very advanced inflammatory state called CRS, or cytokine release syndrome. Well, the good thing is we've now learned how to manage it. We've learned how to identify it; and, importantly, we've learned how to grade it. So, there's now a grading system, 1, 2, 3, 4, 5 and that for every grade, there's something that's actionable.

And the same thing then, another adverse event is this neurologic toxicity. It could be minimal to a little bit of like hand-shaking, a little bit of a tremor, to a confusion state of delirium where someone just really loses the ability to be aware of what's around them. Again, we can grade it; and then once we have a grade, we have a specific set of interventions because we have an actionable event that we can intervene on.

When you tell them though, it's interesting, and again, I understand this 100%. People are used to hearing about intensive care units. They watch it on television. I may need a respirator. I may need the intensive care unit. People are very scared of confusion, delirium, loss of the ability to be who they are, loss of self. I'm going to be curious what Bashi says, but for me, I think I hear that the most is that risk of the neurologic toxicity, uncertainty associated is what scares people the most.

Bashi: I would definitely agree. That is the one concern above all the others that we hear about the most as far as the side effect profile goes for CAR T.

Dr. Maziarz: There are some late effects that happen, that we're now becoming sensitized to and learning. Most of those are all manageable compared to everything. They're all manageable once you know what you're looking for. And by the way, that's another important piece is we do have people over a distance because we have to make sure that we remain available to that patient's personal physician or personal provider, at any given time, they can contact us for advice in "Hey, I'm seeing this. Does this sound familiar?" Sometimes, "Yes, and here's what you should do." And sometimes, "That's brand new" or, sometimes, "That's got nothing to do with it."

Elissa: Yeah. So Bashi, I would like to hear about your role as the CAR T nurse coordinator. How are you helping patients and caregivers throughout this process?

Bashi: So I like to think of ourselves as octopuses. We kind of are in the center of the patient's care with all of our arms outstretched within all the groups and teams. As Dr. Maziarz has mentioned, it takes a whole team to care for these patients; and there's so many involved, and it could be their primary oncologist locally. It could be the team that does the collection, the apheresis, the cell lab, our navigation team who brings the patients in. The interventional radiology team who places the lines. There's just so many pieces to this puzzle, and we all work together so closely to make this possible for our patients.

And then, throughout the rest of the process, of course, our providers, the infusion unit, the Emergency Room, social workers, we're kind of the central coordination, I guess, for everybody to come to from the medical side, depending on where we are in the process and then for the patient as well, so we can be their one point of access for everything that they need and to really be there for them.

And so that's how I view our role. I think it's a very short-lived process. That's the one thing that is a little bit challenging for us is that we don't get to know these patients long term necessarily. But it's such a challenging time, and I feel like patients, as Dr. Maziarz has mentioned, they have so many fears or they're relocating; and they kind of rely heavily on us. So, we get to know them really well and really closely in that fast and furious period of time. And then we get them through the whole process, and then we rehome them is what we call it, so with their primary oncologist again. And, so it's hard to say goodbye after going through all of that with them; but it's an honor to be there for all of our patients and to help get them through this difficult time as best as we can.

Lizette: Yeah, and I know that once CAR T is planned, can you just tell us more about the whole process, the preparation through the initial recovery after T-cell infusion? Patients stay in the hospital for a while, right or now it's different?

Dr. Maziarz: Sure, well the process, it does take long. The way it is now, if we actually take the big global view, is the patient eligible? Is the person who writes for us with the CAR T, we may get a phone call. We may get a patient who finds their way here to ask the question. We will say, "Yes" or "No." We'll say, well let's take the patient we say, "Yes, here's someone we should consider." Well, someone's got to pay for it, so you have to get insurance rule. There's some insurances like Medicare where, yes, you're automatically approved because you're in Medicare and it's covered. Other insurances we have to preauthorize; and based on our experience, it sometimes can take several days or longer to get that authorization to start.

Then, depending on that authorization, they may have a set of tests that are required by the payer, again, to understand that person's position. So, either way, from the time of referral, it may be, on average, about two weeks to two and a half weeks before we're ready to go with, at the earliest.

We have to have disease control during that time, so we're also working with the primary physician about how to keep things under control. And then they have to come in, and that's an outpatient procedure where they sit for one day or sit for basically four hours in a chair; and we just spin their blood. And they get their red cells back. They get their plasma back, but what we're doing is filtering out the white cells because we know there's going to be different populations, but those white cells, are going to have the T lymphocytes that we need.

We then will take those, and there's a very, very highly regulated chain of custody that there will be a courier service to bring it right to the manufacturing site. And we will deliver it to the company to create the CAR T-cells. Honestly, it used to take about a month or even up to a month and a half for the manufacturer. It's now coming down to often 10 to 14 days.

Elissa: Oh, wow.

Dr. Maziarz: Some trials even look a little shorter. You still have to wait. There's a little bit of testing that has to be done to meet the FDA test saying, "This is an effective drug." And once they pass that FDA release, they call us. They're ready to ship it. And then we're, in the meantime, getting ready and getting prepared. Sometimes a patient needs some treatment for that three weeks, not necessarily where we're trying to treat the disease. We're just trying to treat it from getting worse, just to keep it stable because then they're ready to get their CAR T.

When the time comes, we say, "Okay, we have the product. You are ready." Then we actually do use some traditional chemotherapy for usually two or three days, which is actually not necessarily designed at the disease but designed at their own immune system because then when we infuse the CAR T cells, they're hungry. They're already activated. They've been turned on in the company. They're hungry, and they need to be fed. And rather than compete with your own immune system if we get to knock down a person's immune system temporarily, we put the CAR T cells, all the natural factors that feed your immune system then are available to the CAR T; and they will grow, and they will rapidly grow in some cases.

It's been repeatedly shown that we can have 10,000-fold increase occur in the first 7 to 10 days. Those cells want to grow. But every one of them remembers a smart bomb.

So, when it goes in there, it's finding its target. And when it finds a target, it's maybe attacking its target. But then it gets more stimulation. I've got to grow some more because there's more out there. And finally, when the disease burden is now diminished, then they could say, "You know what, I can take a break." And they can go into a rest phase. And then a lot of times we find that they often will take up and do their rest phase where the disease was previously. And so, it's living where it was, and it takes up residence, and it's a squatter. And so, if the disease ever tries to come back, the cells are squatting and say, "Ah, I see you, and I can be reactivated to do my job."

And so, it used to be said that a patient who, once we infuse the cells, they had to be here for four weeks, they couldn't drive for two months. There's all these regulations. There's also requirements of everyone who's involved in caring for the patient of what must be done. But because it's now become such a standard of care, the procedure's gotten so safe, the FDA has released a lot of those rules. And basically, if someone goes through the procedure and they've relocated from somewhere. In 14 days, they've never had some of those very early toxicities, they have the approval to go home. And then we will continue to connect with them over time in a distance.

Now, there's one little caveat still. There are some long-term side effects, but the FDA still wants to learn more. We do have a commitment to follow somebody for 15 years.

Elissa: Wow!

Dr. Maziarz: Anybody getting a gene therapy product, there is a commitment from the center, by the treating team that we will do everything possible to collect the data and even once a year touch base to say, "How are you doing? Anything new? Is there anything I need to be aware of or worried about?" And it's just part of the responsibility.

But then, as Bashi was saying, sometimes we become really close to people. They go home and it's like, "Hey, you know what, we may see you again. That's our goal, to see you again; and our goal is to have new things if your disease comes back. And if it doesn't come back, that's fantastic. That's what we wanted to achieve, but we can continue to connect with you long time."

Elissa: Okay. So, one thing that we don't often talk about with CAR T-cell therapy is the aftercare; and, Bashi, maybe you could step in here. Could you tell us how you are working with the patients after the procedure and maybe in that initial recovery?

Bashi: Yes, absolutely. And I just wanted to add, as well, as far as the hospitalization goes, just to add more excitement to what we're learning every day, when these products first came out, everything was in the hospital as far as the infusion goes. And patients would stay for at least five to seven days afterwards. And now we've come to a point where we are infusing CAR T-cells on an outpatient basis with almost every product that we have.

Elissa: Oh!

Bashi: There are some, of course, possibilities where the patient is not stable enough or if we just can't fit it in for some reason. But otherwise, we are now infusing outpatient and then admitting patients quickly if we know the onset of the side effects Dr. Maziarz was talking about, the cytokine release syndrome. Those happen really quickly within a few days. Then we admit them that night; or with some of our other products, like CARVYKTI®, we know the onset is delayed around day six or so, so we admit them to the hospital a bit later.

Elissa: So, they need to then be living within a short distance of the hospital?

Bashi: Yes. So, we still require everyone to be within 50 miles of OHSU, at least for the first 14 days. And we do, ask patients to be prepared for the first 30 days, sometimes even longer if they need infusions or transfusions and if the local oncology clinic is unable to, for instance, provide three days a week of platelet transfusions or what it may be, so sometimes we hang onto patients to make sure it's safe for them to go home. But otherwise, we do try to get them home as quickly as possible. But that initial time, especially in the first two weeks after the infusion, we do ask them to stay within 50 miles of OSHU.

And then the aftercare, it depends, again, on the stability of the patient, how many side effects they had. But again, we do want them to go home as quickly as possible, especially if they're coming from a distance to kind of go back to their communities and their homes. But I would say it also depends on what patients look like when they're coming in, how much disease do they have onboard. Hopefully, we're controlling some of that with that bridging therapy, as Dr. Maziarz has mentioned, between the collection and infusion.

But then how fit were they before with good diets, exercise, amount of stress, sleep, all those things? Are they still coming in, recovering from a heavy treatment they've received? So, all those factors definitely play a part, and then how active do they continue to stay throughout?

So we, as nurses and social workers, we definitely encourage our patients to continue remaining as active as they can, get good sleep, but get some exercise, lower that stress level, lean in on your community, lean in on your friends, your family to help you through this process. But oftentimes they're able to do their own activities of daily living. They can continue cooking with their caregiver. They can do "clean chores" we call them, like folding laundry so that they can remain as active as they can, and that definitely helps with that recovery period.

Elissa: So, now, a little bit of an exciting part, I hope. After the whole process is completed, how and when do you know if the CAR T-cell therapy was successful?

Dr. Maziarz: I think the question is what's the definition of success, first of all, because I mean if someone has a large mass growing off of their neck and nothing has stopped it, once it starts to shrink within days, the recipient is like ecstatic because, nothing else has worked. And now they start to believe and they start to benefit.

What we look for is, and we try to have measures that will be reproducible. We look at what we call partial responses, which is it's at least in probably close to a 75% reduction in total volume. What we look for, specifically, is a complete remission where it still may be there, but I can't detect it. So, that's the important one is can we get to complete remission? And in all these treatments, all the drugs we mentioned earlier, we do gain complete remissions.

Elissa: Wonderful.

Dr. Maziarz: Then it becomes how long and when do I think it's not real? Now, traditionally we call a cure at five years if we don't see something. And what we've learned is there's a lot of patients who gain complete remission by 30 days. And then by 90 days, if they're still in remission, that predicts for six months. If they're in remission at six months, that predicts for remission at three years. And now we know if you're in remission at three years, it predicts for remission at five years.

We now have for three products in three indications where we know that we have five-year disease free for large populations where we're curing 40 to 50% of people we wouldn't have said was curable before. And so, I always say, five years is that target. That's what most people believe. But we do know that in a lot of cases, it's 18 months to 24 months. If you're free of disease, there's a good chance it's going to be long term. Now, that's about lymphoma and leukemia.

I would tell you that we've been a little hesitant as a community to say much about myeloma because myeloma has a long history of being a chronic disease that comes and goes, comes and goes, comes and goes. But I would say one of those exciting breakthroughs is there's two approved products and multiple products in development. But one of those products came out with that 50% of people treated were in remission at 2-1/2 years. So, that's excellent. That particular study, the patients had gone through three or four more or five or six lines of therapy before they were eligible.

Last June, a report came out to say of the 50% who were free of disease at 2-1/2 years, 60% of them or 30% overall were still free of disease at five years. And similar to lymphoma, rather than see a steady, continuous recurrence rate, we were starting to see that people weren't recurring, and there may be a plateau across time. The first inkling that even myeloma may be something that can be permanently eradicated by CAR T. It's still too early to declare, because that's the first observation. We need to follow that for the next 2 to 3 years and see what we learn. Once that's the case, I mean everyone's excited.

Elissa: Yeah, that is so exciting. Wow!

Lizette: Yeah, that's really good to hear. I want to continue this discussion about the future of CAR T-cell therapy. So, are there any clinical trials or newer types of CAR T-cell therapy that you're particularly excited about?

Dr. Maziarz: Well, first, I would just say that we got to where we are because of the commitment to do it scientifically in clinical trials. It started with a few centers who decided to seek research grants, seek philanthropy to test the concept. And what was a shock, honestly, is going back to around 2010 is when industry decided to spend a lot of money to invest in a single-person therapy. The industry is all about mass production, and this is, every drug that's produced is unique to an individual. But industry did get sponsored and get involved, and industry sponsored, a lot of the trials that led to FDA approval.

So, we're part of a clinical trial network that unites many centers across the country who are putting patients on clinical trials; and there's multiple CAR T trials that are now funded by the NIH (National Institutes of Health) that are uniting the research community across the country so that community isn't just the Northwest.

I'd say the field is accelerating, not slowing down, because there's so much belief in it now that everybody wants to work together and work on this.

Second, I will have to point out that recently the FDA has said, you know what, we've made so much progress, we're going to need to do some testing against all the new products. Have to prove their better than what we have already. So, a lot of the original approvals were based on nonrandomized, observational, interventional trials for this disease, this cohort. Let's see what happens? And boy, it was better than what we have known historically. So, it changed the natural history.

But now we have products, so we will see clinical trial evolution rapidly coming out of the FDA saying, "If you're going to develop something new, you've got to prove it's better than the ones that we have." And so, we are going to see that evolution. I think if I talk about other types of therapies, the ones we have now I expect they're going to be replaced by better yet products that's going to deliver even higher response rates. I mean earlier application is critical. Why wait till third or fourth line, and we are testing CAR Ts to consolidate first-line therapy now. We're bringing it way forward.

I think if I had to pick something, there's a lot of discussion about off-the-shelf, where healthy donors will come in and have their cells made. And we've been part of some of the off-the-shelf studies. They're interesting, it's rapid, it saves time. So, I would say so far they haven't yet materialized as a standard of care because you still are working from a product that came from somebody else. And so, if you basically get rid of your own disease, it turns out that as you get healthier, your immune cell may see those cells as foreign and get rid of them. So, persistence, which we know happens with your own CAR Ts, persistence may not yet be solved if you have a donor CAR T.

Now, what I would say is, to me, is the most exciting right now and this just came out of the hematology meetings last month. On the very last session, they call it late breaking abstracts, where someone has brand new data. I've got to show it. And there's a study from Australia, and there's a lot of attention now. We create products by collecting cells, sending them elsewhere to be manufactured, and it takes about three weeks. Well, people are asking, "Why can't I do it directly in the body where I can inject you with something that will deliver the DNA and create the CAR T in your body?" And so, this is a really cool study where there's a group and they planned it as a safety study. So, there's three phases. Phase 1, Phase 2, Phase 3, which is increasing the dose at every step.

And so, when they started with the earliest phase, what they thought was the lowest dose, and what they did is they had the DNA for the virus that will help make the T cell and create the T-cell construct; but they hid it in a capsule. And it turns out it's another virus capsule that is genetically engineered to bind T cells in your body so that there's no DNA from that virus. It's just a capsule. So, the capsule binds only your T cells, but then it packages the carrier DNA to change the T cell.

So, I look at it as the Trojan horse.

Elissa: Yeah.

Dr. Maziarz: The virus capsule is the Trojan horse, and inside is the DNA you want to deliver, and they're delivering it. Well, this was what was shocking is the first three patients at the lowest dose level all responded, It was all from myeloma, including a patient who got into complete remission already. So, they went and reported a fourth dose, a fourth patient which is dose minus one where they reduced the dose further by 70%; and still, that patient is down, reported as responding.

So, in an early level trial, 4 of 4 patients treated have responded. We do not know if it's going to last, but they did not need any of that chemotherapy, that lymphocyte-depleting chemotherapy ahead of time. We didn't have to keep the cells happy and healthy because they're in your body already, and then at the moment, interestingly, the toxicity level has been relatively low.

And so, it seems like it's a safe approach. So, exciting, brand new. You know, it's future. I don't know, but boy, that ones got my attention.

Elissa: Wow, that is just so cool. I love hearing about that and how exciting for the future potential of this.

Now, our final question today, on our patient podcast homepage, we have a quote that says, "After diagnosis comes hope." What would each of you say to patients and their loved ones to give them hope if they are looking into CAR T-cell therapy?

Dr. Maziarz: So, I would say, again, we live this. So, we have tools; and I've been doing this for many years, and we just are looking for the best tool.

Elissa: Yeah.

Dr. Maziarz: And you can sit back and say that we're going to focus on treating your disease. My first goal was to make something that's potentially life-threatening or even of an acute process. I'm going to see if I can make it a chronic disease. So, I'll be happy with that. And then if we can go from chronic, then can I cure it?

Elissa: Yeah.

Dr. Maziarz: So, you can hope for a better future. What I'm going to hope for is that I can deliver something that's going to change the natural history of your disease, improve your life on a daily basis, and, importantly, we're going to be available to you as new tools come around. If this tool didn't do its job, we're going to have the next one ready.

Elissa: I love that. Bashi?

Bashi: I would hope to give patients what they would like from life after diagnosis. So, whatever their hope may be, whether it's to prolong their life, it's to be in complete remission, it's to get them through the next phase of their life. It's to get to their daughter's wedding or whatever it may be that their hope is, I would say that we are hoping to give them the gift of what their wish would be, depending on whatever the treatment would be or supporting them through their journey.

Elissa: Yeah, that is so important because I think when you're in the thick of things, it's hard to think about life after cancer or life after treatment. And it is so important to think about those things that you want to get back to, and you want to be with your family and travel or just have general health. And so that's very important.

So, thank you both so much, Dr. Maziarz and Bashi, for joining us today and telling us all about CAR T-cell therapy and the really exciting advancements and where we can see it going in the future. I think you've given so much hope to patients as to this therapy and where it might be able to go. So, thank you again so very much to both of you.

Dr. Maziarz: Well, I'll say thank you to Blood Cancer United as a group that's committed to sending messages because you will reach more people in a single moment than we can. And so, you are making a difference; and you have to take credit for the work that you do to bring the message that people can have and find these options are waiting for them.

Elissa: Oh, thank you so much.

Bashi: I second that, yes, and the support that you provide for all our patients, as well. We turn to you quite often for everything from education to financial support to our patients. So, yes, very grateful to you all.

Elissa: Thank you.

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

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

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

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