LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Emerging Research in Lymphoma and Myeloma'

Description:

Join us as we speak to Dr. Peter Reidell and Dr. Benjamin Derman from University of Chicago Medicine, about the latest research coming out of the annual meeting of the American Society of Hematology (ASH). In this episode, we discuss new treatments on the horizon for lymphoma and myeloma. The doctors share how innovative therapies such as CAR T-cell therapy and new combinations of medicines are showing significant promise, providing further hope to patients.

Transcript:

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

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

Elissa: Today, we will be speaking to Drs. Peter Riedell and Benjamin Derman about lymphoma, myeloma, and the exciting emerging treatments that have come out of the recent annual meeting for the American Society of Hematology or ASH.

Dr. Riedell is an Assistant Professor of Medicine at the University of Chicago. He specializes in the care and treatment of adults with all types of Hodgkin and non-Hodgkin lymphoma and is an active clinical researcher for several ongoing clinical trials to treat aggressive lymphomas. As the Director of Clinical Research for the Hematopoietic Cellular Therapy Program, he leads the University of Chicago's efforts in stem cell transplantation and CAR T-cell therapy for lymphoma.

Dr. Derman is a clinical researcher and Assistant Professor of Medicine at the University of Chicago. His clinical focus is on the treatment of patients with multiple myeloma using state-of-the-art diagnostics and therapies to guide patients to long-term durable remissions.

Dr. Derman is also an investigator on many clinical research trials focused on targeted therapies and CAR T-cell therapy. Currently he is focused on identifying strategies that can lead to a possible cure for multiple myeloma, including using testing minimal or measurable residual disease, also known as MRD to guide decision-making.

Welcome Dr. Riedell and Dr. Derman.

Dr. Peter Riedell: Thank you. Thanks for having us.

Dr. Benjamin Derman: Thanks so much.

Elissa: So, we are so excited to talk to you both today about the latest advances in lymphoma and myeloma coming out of the ASH annual meeting that was held in December of 2021. To make sure all of our listeners know about the diseases we are going over today, let us do a brief overview. We'll start with Dr. Riedell. Could you tell us in general what Hodgkin versus non-Hodgkin lymphomas are?

Dr. Riedell: Sure. So, Hodgkin's and non-Hodgkin's lymphoma are both cancers of the white blood cells, and essentially these are approached a little bit differently; but when we think about them as diseases, typically we can divide them into different subtypes based on whether they're more aggressive and may need treatment at the time of diagnosis or whether they're more indolent or slow growing and potentially more of a chronic disease for a patient.

And then specifically Hodgkin lymphoma is a little bit different in terms of both the patients that may be afflicted with that, and our treatment approaches compared to non-Hodgkin's lymphoma; and there's a number of different treatment options for both of those arenas and certainly some exciting updates that were presented at ASH in relation to that.

Lizette: Thank you. And Dr. Derman, your clinical focus is on multiple myeloma. Can you explain to our listeners what multiple myeloma is?

Dr. Derman: Sure, yeah. Multiple myeloma's, of course, a blood cancer; but the cell that's involved is a little different than the lymphomas that Dr. Riedell just mentioned. So, these involve plasma cells, which are actually very, very mature B-lymphocytes. The job of these cells are normally to make antibodies; but in this case, of course, in myeloma, these cells have undergone a series of mutations such that they've become cancerous.

And myeloma has some very unique presentations. We know that it can affect the bones, it can affect the kidneys, it can affect blood counts. So, it really requires a full scope view of the human body to really treat this disease and prevent a lot of the manifestations that we can see from it.

Elissa: Now, Dr. Derman, one of your clinical focuses is on amyloidosis. I'm curious, since we are talking about the latest advances in therapies, and that is a particular diagnosis that's not widely talked about but that several of our myeloma patients have developed. Could you tell us a little bit about what that is, how it is linked to myeloma, and if there have been any advances in treatment.

Dr. Derman: Sure, so I think the thing to remember is that we're talking about plasma cells being the issue here, both in myeloma and in amyloid. So, they are related disorders.

In some cases, about 10% actually of myeloma cases also involve light chain amyloidosis, so that's the one that we're going to be talking about here is light chain amyloidosis.

So, the way to think of it is that they sort of arise from the same issue, which is that you have plasma cells that have become cancerous. I think the major difference here, though, is the way in which they present. In amyloid, for instance, patients typically don't have quite as much amount of disease in the bone marrow when we check it or even in the blood when we check for the proteins that are being made by these cancerous cells. The difference is that in amyloidosis, the proteins that are being

generated often get misfolded. They can kind of jumble together and often deposit themselves into very important organs like the heart; the kidney; even the nervous system; the GI tract, including the stomach or the colon, the small intestine. So, these things can present themselves very differently than myeloma where you may have heart disease, you may have diarrhea, weight loss, neuropathy, meaning numbness or tingling that's unexplained.

So, amyloidosis is often actually a more challenging diagnosis to make, but we do have patients, of course, who actually have both because the underlying process is ultimately the same; but the way the disease behaves is actually a bit different.

We've actually had a lot more focus on light chain amyloidosis in the last few years.

One of the things that has really made a big difference is the addition of newer targeted therapies or immunotherapies in myeloma. In particular, there is a signal on the surface of certain plasma cells, in particular both in amyloid and myeloma called CD38. And there are actually two drugs that are currently approved that target CD38, daratumumab and isatuximab.

Now there was a Phase III study, really the highest-level study that we can perform that compared the standard of care, which is usually three drugs involving cyclophosphamide, bortezomib, and dexamethasone with that same regimen with the addition of daratumumab. The study is called the ANDROMEDA study. It was published in the *New England Journal* earlier this summer, and we're continuing to get new updates as time has gone on, including at ASH this past December.

And what's really interesting that we see here is that the addition of daratumumab seems to improve not only the responses of the disease, but it's also improving organ response rates. So, I just mentioned to you that the heart and the kidneys, in particular, are the ones that we worry about being affected in amyloidosis. Well, actually, the addition of daratumumab nearly doubled what we call the cardiac

response rate, meaning improvement in some of the parameters that we look at of the heart.

So, at six months after therapy, you went from 22% of patients without daratumumab to 42% who had a cardiac response rate. And at 18 months, we have 53% of patients who actually had a cardiac response rate with daratumumab.

Similarly, with, when we look at the kidney response rates, it was 58% after 18 months. So, there's a couple of interesting things here to note. One is that the addition of daratumumab is improving these organ response rates, and you have to give it some time. These are not things that are going to happen immediately. You have to wait that six months to really see the full benefit.

But one of the things that I'm looking at is the improvement between 6 and 18 months is not really that profound, so I think what it means for us, in terms of how we approach our patients, is that that six-month mark doses seem to be very key. The progress that we see after those six months, which is really the most intensive part of the therapy, is really going to be one of the most important things.

But this, to me, is the new standard of care for light chain amyloidosis; that the inclusion of this CD38 monoclonal antibody, that's what daratumumab is extremely important in this population. And I think, when we look at long-term outcomes, we don't have that yet. Right, that's the something that we're going to have to wait and see.

But certainly, one of the big questions is the inclusion of autologous stem cell transplant in this disease. So traditionally we've used a very high dose of chemotherapy and used a patient's own stem cells to rescue them, to allow them to recover from this chemotherapy more quickly and allow the chemotherapy to actually do its job, right, which is to kill any remaining plasma cells that are there.

Now it's a little bit challenging to do transplants in many amyloid patients because of the heart issues, the kidney issues. These are very important organs; and we're giving a very toxic level of chemotherapy to patients.

So now the big question is if we have this great new standard of care with four drugs, which we call quadruplet regimens here, what is the role of stem cell transplant? That's going to be the question that we're going to have to answer in this next generation of studies in amyloidosis.

Elissa: Oh, that's great. I'm really excited to hear that there have been advances. I hope that myeloma patients listening that also have amyloidosis will really benefit from hearing that.

Lizette: Yeah, definitely. And Dr. Derman, you also mentioned MRD. So MRD, minimal or measurable residual disease, and I'm always confused as to which one to say. I know that it started as minimum residual disease. Now I'm hearing more so that it's measurable residual disease. Can you explain that to our listeners?

Dr. Derman: Yes, absolutely. So, I think, either term is fine. The field is sort of moving towards using the term measurable residual disease as a more accurate term. But just to explain a little bit about what MRD is, and this is not just unique to myeloma. We use this in various disease states, various blood cancers.

Really what we're talking about is low levels of cancer cells that we previously would never have been able to detect with conventional studies. So, I want you to think about this. Many of the listeners here will probably have undergone a bone marrow biopsy, and the thing that you don't know is what happens after those samples are taken?

So, what happens is those samples actually go down to a pathology lab, and we have our pathologic wizards, pathologists. They have a career where they just look at tissue slides and to figure out what is going on beneath the surface.

For instance, I think we have some of the best pathologists in the world, if not the best, even they can only look at up to maybe 1,000 cells. It's a pretty low-level look at what's going on.

And when you are having very effective therapies that are really getting rid of the majority, if not all of the disease that might be present, the question is, well, how do we know if there's any disease left or not?

So there have been tests that have been developed that can be, performed on the liquid sample that's taken from the bone marrow called the aspirate; and we can do a variety of tests to look for residual disease or these low levels of cancer cells. The question for the field has been what is the significance of somebody who does or does not have disease detectable by these very sensitive tests? And then secondly, what can we do about it?

So, that first question really has been answered for the most part in myeloma. We know that patients who do not have detectable disease, in other words, MRD-negative, seem to have their disease stay away for longer; and in many cases, those patients actually live longer compared to those who still have detectable disease, even at very small amounts.

So that's a really important piece, but I think the big question that both clinicians and patients are asking me in clinic is, "Well, okay, can I do anything about it? If my test is negative, does that mean I can come off of some treatment? If my test is positive, should I continue on my treatment? Do I have to escalate treatment?" These are answers we don't have yet, and the next generation of clinical trials really need to answer.

Lizette: Yeah, I know that for myeloma, as you mentioned, that we do have a lot of information about MRD. I'm curious, Dr. Riedell, just because I'm not sure if MRD is established in the lymphomas.

Dr. Riedell: So certainly, MRD is actually something that we've been using in various subtypes of non-Hodgkin lymphoma now for a few years; and there are now a couple actually FDA-approved tests for patients with different subsets of non-Hodgkin lymphoma. Specifically, this is a test that we use in patients with one subtype known as chronic lymphocytic leukemia or CLL, along with patients with mantle cell lymphoma. These are tests, which are available commercially, FDA approved, and typically are paid for by a patient's insurance. And so, this is something that we're more frequently utilizing in the clinical space to get an understanding of how deep a patient's remission may be. And kind of dovetailing on some of the points that Dr. Derman discussed is what we're still trying to grapple with as a field is how do we use this information to actually, potentially make clinical decisions?

One of the areas where I think we're trying to move in the treatment of various subtypes of cancer is knowing how deep of a remission we can achieve with some of these therapies. And then also at what point can we potentially stop some of our therapies? There's a common paradigm in the treatment of various types of cancer; and this is not just relegated to hematologic malignancies but a lot of other cancers as well that we treat patients with a particular regimen until we either see that they're not responding to it anymore and the disease starts growing, despite us treating them, or we stop therapy because the treatment is too toxic.

But it would be great if we were to be able to have a better gauge or metric to know that, with our most sensitive test, we can't find any evidence of disease and we can then stop therapy. And that's really where we're trying to get, as a field, to kind of use this tool to better understand the status of patients' disease and then to potentially inform treatment decisions, whether to continue, to stop, and so forth.

Elissa: That's a lot of really good possibilities for the future. Now let's talk about emerging research from ASH. What are you really excited about that you heard about in December? We'll start with Dr. Riedell and lymphomas.

Dr. Riedell: Sure, so I would say for lymphoma, this past ASH meeting was probably the best it's going to get; and I say that because there were many really impactful studies that were presented during that meeting. And, in fact, one of the trials that we participated in here at the University of Chicago was part of one of the plenary sessions at ASH. And to kind of get into some of the details of that, in diffuse large B-cell lymphoma, which is the most common aggressive subtype, the typical treatment paradigm in patients that have disease which is either refractory or doesn't respond to first-line therapy or relapses after initially responding to first-line therapy, in that population of patients we are traditionally treating those patients with a second cocktail of chemotherapy drugs with the intent of achieving response and then moving them forward with an autologous stem cell transplant to kind of consolidate that remission and ideally lead to improved outcomes in patients.

But what we've learned is that that approach is not a one-size-fits all; and there's certainly patients who do benefit from it. But there's also a large proportion of patients that don't benefit from it. And particularly those are the patients that don't respond to initial first-line treatment approaches and those that may relapse early after concluding their first treatment approach.

And so, during this ASH meeting, we had the presentation of three different trials from three pharmaceutical companies which compared the standard treatment approach of salvage chemotherapy followed by an autologous stem cell transplant with a different form of therapy called CAR T-cell therapy or chimeric antigen receptor T-cell therapy.

And CAR T-cell therapy has now been FDA approved in the third-line setting in patients with diffuse large B-cell lymphoma dating back to 2017, and it's certainly been incredibly impactful in that treatment setting. And what these three large clinical trials were trying to do is evaluate and see if we can actually improve outcomes by moving CAR T-cell therapy earlier in the treatment paradigm and using it in the second-line setting as opposed to in the third-line setting.

And so, each of these trials compared again our traditional approach with salvage chemotherapy in an autologous stem cell transplant to CAR T therapy. And two of the three studies which were presented during the ASH meeting actually showed positive results. And really to kind of get further into those details, it showed that those patients that got CAR T-cell therapy compared to getting salvage chemotherapy, that a higher proportion of the patients ended up receiving definitive treatments. And there was also an improved progression-free survival or more patients who were alive and without evidence of lymphoma progression and also a hint that there may be improvement in overall survival for patients who received CAR T-cell therapy over our standard autologous stem cell transplant approach.

This certainly does set the stage for us potentially having CAR T-cell therapy approved in the second-line setting for patients, which we may see as early as this coming summer.

Lizette: Wow, I know that a lot of our patients and caregivers call us, and they are asking when we think that CAR T will become first-line therapy.

Dr. Riedell: Yes, that's also a really intriguing question and something certainly that the field is moving towards. There was also another study which was presented at this ASH meeting. It was an update of a ZUMA-12 trial which actually evaluated the utility of CAR T-cell therapy in the first-line setting.

And where they really looked at it was in a population of patients with very high-risk disease; and they defined that based on different molecular markers but also based on patients who failed to achieve a remission after just two cycles of chemotherapy. And in that population of patients who didn't achieve a complete remission after two cycles of chemotherapy, they then went onto receive CAR T-cell treatment; and we saw some really encouraging results in terms of outcomes in that population of patients with close to about 70%+ of patients achieving complete responses.

Certainly, that's something though that in order for us to firmly adopt that treatment in the first-line setting, we would need to do a fair comparison of that approach to our traditional approach to really get a better understanding of which one is better. But the ZUMA-12 study does at least kind of set the stage for trials like that to be formulated and certainly lean more towards the expansion of CAR T-cell therapy into earlier lines of therapy.

Dr. Derman: Well, Dr. Riedell, I had a question. This is something that comes up in our clinic as well. As you're talking about autologous stem cell transplant and CAR T therapy, maybe for our listeners, could you talk a little bit about what the difference in patient experience might be between those two and what patients might be able to expect?

Dr. Riedell: Absolutely. When we utilize autologous stem cell transplants in lymphoma, it's generally utilized as a consolidation approach. What I mean by that is that basically patients would need to demonstrate that they're sensitive and that their disease, their lymphoma or even multiple myeloma, that their underling cancer is sensitive to chemotherapy and, thereby, is shrinking and responding and going away.

When we incorporate high doses of chemotherapy, we rescue the patient's immune system and their hematopoietic system with these stem cells. And certainly, there's a good deal of toxicity associated with that approach. Essentially when we provide these high doses of chemotherapy, the intent of it is to eradicate any remaining or residual cancer cells which may not be apparent on our imaging studies, may not be apparent on our bone marrow biopsies or other blood work, but we know they're probably around.

The intensity of that chemotherapy is also to such a degree that it wipes out their immune system, which necessitates the need for the transplant. But you can also imagine that intensity of chemotherapy can be associated with significant toxicities; and we're seeing things like low blood counts in patients, risk of infectious

complications, need for blood transfusions, things like nausea, vomiting, diarrhea. Typically, those side effects do improve with time; and most patients are discharged from their hospital stay typically about 2-1/2 weeks after their treatment.

But in terms of recovering to the point where they're able to return to their regular everyday life and return to work, that's usually measured on the magnitude of weeks. And most patients, at least in my practice, wouldn't be able to return to work until probably about three months or so after they receive their autologous stem cell transplant.

I think the one distinct feature that kind of differs from CAR T-cell therapy is that the intensity of CAR T-cell treatment in terms of the chemotherapy that we use for that approach is lower. And also, the hospitalization in many respects is shorter. And therefore, that does afford patients the ability to, in many instances, return to work or at least return to some of their regular, everyday activities a little bit sooner than patients who underwent stem cell transplants.

And specifically, this was looked at in a little bit more granularity as one part of the ZUMA-7 study, which was one of those three pivotal trials that I had discussed comparing autologous stem cell transplant to CAR T-cell therapy. And what was presented at ASH showed that, in patients who received CAR T-cell therapy, the trajectory of return of their quality of life was actually a lot more rapid than it was in those patients that received stem cell transplant. And so that kind of speaks to the toxicity burden being lower with CAR T-cell therapy compared to autologous stem cell transplant.

Elissa: Now are we also looking at different long-term complications as well? So we all know that at least allogeneic stem cell transplant can have GVHD, or graft-versus-host disease. Are the long-term complications after CAR T, similar, different, generally not any?

Dr. Riedell: So certainly, it is not without its own potential complications or at least risk of complications. One of the things that we do see with CAR T-cell therapy is that some patients may have what we call, prolonged low blood counts; and sometimes that is seen particularly in patients that have a lot of involvement of their bone marrow from their underlying cancer and patients that may have received a number of prior treatments leading up to their CAR T-cell therapy. And so that may require close monitoring their blood counts and transfusion of blood products.

There is also a risk of secondary malignancies where the treatment that we're providing may potentially damage the DNA and predispose those patients to other types of cancer, particularly things like acute leukemias. That is something that we, at this point in time, haven't seen an incredibly high signal of that's been of concern; but when we compare our track record with something like CAR T-cell therapy to something like stem cell transplant, it's very different.

We've been doing stem cell transplants now for decades, whereas CAR T-cell therapy's only been FDA-approved since 2017. So, we do need a little more time to be able to kind of see, with longer follow-up, will we see the emergence of complications more down the road?

Dr. Derman: One thing I'll add to that is, most of the time when we're talking about, in both myeloma and in most cases in lymphoma, is autologous stem cell transplant. So, something like graft-versus-host is typically not something that we're as concerned about because that's usually something that we'll see with allogeneic stem cell transplantation, meaning from another donor.

The important thing to remember here is in regards to what Dr. Riedell said in terms of secondary malignancies. In myeloma actually, even with a transplant followed by maintenance therapy, we see much higher rates than what our lymphoma colleagues might see or what we would see over the background rate for regular people.

So that's something that is a big concern; that risk can still exist many years out from completing transplant or while on maintenance therapy. It's something that we do watch out for. Although it is rare, overall, it is still something that we are concerned about and have to look for.

Lizette: And Dr. Derman, since you mentioned myeloma, what are you excited about from the ASH meeting?

Dr. Derman: We didn't get quite as much attention as our lymphoma colleagues got this year.

Lizette: Oh, I'm sorry, aww.

Dr. Derman: It's okay. Most years, myeloma gets all the attention. But I'm glad that lymphoma got a little shine this year.

There were a lot of important things. I think you could take your pick. I'll just run through some highlights for me.

If you take looking at before patients actually get myeloma, when they have precursor states, which we call MGUS or smoldering myeloma, there is this amazing study going on in Iceland right now where they are screening about half of the adult population who are healthy adult not known to have any issues in terms of myeloma. And what they're doing is screening for these precursor disorders. And so, we're really getting a lot of information about what is the natural incidence of MGUS, this precursor, monoclonal gammopathy of undetermined significance, in this population.

Well, I say precursor because these are patients who don't have any manifestations of myeloma but do have actually the beginnings of that disease. If you were to do their bone marrow biopsy, you would see some of these abnormal plasma cells. And when you check the blood, you see these abnormal proteins in the blood.

And so, what we're finding out is that the prevalence of MGUS increases with age. That's something that we did know about, but, you know, it's as high as 12 to 13% in patients who are above age 80. But when you look at ages 60 to 79, it's somewhere around 6%. And patients aged 40 to 60, it was around 2%. The question is, does it help to screen and to find these things early? That's the real big question, and I don't think we're going to have that answer for many, many years; but this is the study that will help answer whether screening makes sense.

If you look at smoldering myeloma, which is in between MGUS and myeloma, so these are patients who have a little bit more disease than our MGUS patients, what we're finding is that the prevalence of this is actually much lower overall. But what we're trying to figure out is, is there maybe a population of patients who we know are going to have a higher risk of having this MGUS or smoldering myeloma? In the Iceland study, out of, I think it was something like 150,000 people, they only screened about 75,000. About 180 were diagnosed with smoldering myeloma, and these are the patients who are more likely to go on to develop multiple myeloma in the near future. We're going to be looking very closely at that.

A wonderful study being done right now called the PROMISE study; and it's looking at screening adults who are 40 and older and who either self-identify as black or have a family history of blood cancers in two or more relatives in the family. And I encourage anyone who's listening who this might apply to, to enroll in this study; and we're learning a lot of information from it. And what we're finding is that MGUS is actually present in maybe 10% of these patients. This is a far cry from the 2% to even 6% that I mentioned before.

So, there's definitely, I think, going to eventually be a group of patients who we may screen for; but at this point, I don't recommend people just going out and getting screened. It's going to cause a lot of anxiety, a lot of added cost to healthcare expenditures; and I don't think we're going to see the benefits of that. But there's

probably a population of patients who are known to be at high risk who we should be considering.

Elissa: That's really interesting.

Dr. Derman: It is, and this is not a disease that we thought originally was something that maybe the risk is transmitted through families. It's not like breast cancer or ovarian cancer, but actually that may not be true.

We saw some data this ASH that close to 10% of patients who are diagnosed with myeloma, likely had a predisposition to developing myeloma, a genetic predisposition. So, this is something that they inherited from mom or dad or, that made them more likely to develop myeloma. So, I think, those are the patients whose family members we may want to be screening to figure out how we can diagnose them earlier and figure out interventions that may be able to help them.

When we talk about patients who are newly diagnosed, I mentioned quadruplets in the amyloid space. This is all the rage in newly diagnosed multiple myeloma. So those anti-CD38 monoclonal antibodies, we're seeing those being incorporated into what we call the frontline regimens.

So, for a long time now, our standard of care has been the incorporation of bortezomib, lenalidomide, and dexamethasone, which we refer to as a triplet. Now the quadruplets are coming, so the addition of daratumumab and isatuximab, we're starting to see these results. So, we saw a longer-term follow-up with daratumumab plus VRD, that triplet I mentioned. And we're seeing that the response rates are certainly better with the quadruplet. And now, interestingly, we have some data on that progression-free survival. Remember, that's the time that patients are alive and free of their myeloma coming back.

And then we also have some data now about what to do after transplant. So, we've used lenalidomide for a long time. That is still the standard of care. Now the question

is, well, we have these anti-CD38 drugs that I mentioned. Can we use those after transplant? So, we have this French study called the CASSIOPEIA study that presented on comparing this daratumumab drug to those who actually went on observation alone and found that it did benefit patients who did not receive daratumumab at the beginning of their treatment. But if patients got several cycles of daratumumab before transplant, the benefit to daratumumab wasn't so obvious. In fact, they did not really show a benefit for those patients.

So, now the question that we're going to be dealing with is which agents are the best ones to use after transplant? Is two drugs better than one? And how do we make sense of that? Because I think the biggest question in myeloma is patients are living a long time now. And to show that drug A leads to better survival than without drug A is getting harder and harder because we have so many good therapies that are available if patients should progress.

So, it makes interpreting these studies actually more challenging. It's a good problem to have in the end but one that we have to grapple with. So, if you think about it like this, if I don't get drug A now but I get drug A later on, is my outcome the same? That's the answer that we don't have yet. We don't know how to answer that question.

Elissa: We actually spoke with a CLL patient in a recent episode, and he was talking about how, he has to almost kind of pick and choose because if he uses this one drug, he won't be able to use it again in the future. But then there will be another drug later and another drug later, and so he wants to kind of pick and choose what he can use because he might not be able to reuse that one if he tries something and later that fails. So that's really interesting.

Dr. Derman: It would be easy if we knew that there was just one way to do things. And as long as you follow that one way, you follow that recipe everything turns out fine. In myeloma at least, it's a little different than lymphoma where we know that for

non-Hodgkin lymphoma, for aggressive lymphomas, something like R-CHOP is really kind of the right way to do it in almost all cases. In myeloma, we have lots of different regimens to be choosing from; and some of it is dependent on, what kind of comorbid conditions does the patient have? What are the preferences of the patient? What are the preferences of the physician? What do they feel comfortable providing to the patient?

So, what I encourage people to think about though is that your best chance of this long-term durable response is likely going to be your first line of therapy. That's not true in all cases, but in most cases, that's the truth. So, really, you want to try to put your best foot forward at the beginning.

We talked about MRD a little bit and quadruplets, so now I'm going to combine those two. There was a wonderful study that just got published in the *Journal of Clinical Oncology* but was presented at ASH as well called the MASTER trial. And what this did is combined a four-drug regimen called dara-KRd, daratumumab, carfilzomib, lenalidomide, and dexamethasone with transplant.

But they actually did incorporate MRD testing into the treatment protocol, and patients who had two consecutive tests that were performed for MRD that were negative, that were undetectable, were able to actually undergo discontinuation of all their therapy. They just stopped. It's every patient's dream, right, to be able to stop treatment. And now what we're trying to figure out is what happens to those patients over time.

So, what we have seen so far is that in the first year to year and a half, very few patients have had their disease come back, which is really promising. I think as time goes on, we're going to want to see what happens to those patients because we really have to look at four, five, six, seven years down the line. And also, this technique though does not seem to be the best way to do it for patients who have very high-risk disease or ultra-high-risk disease. These are patients who have multiple mutations that suggest that their disease is not likely to respond to treatment for very long.

And, in fact, even in this study with very powerful treatment, once you step off the gas, the disease figures out a way around it. So, it's not a one-size-fits all. It's definitely unique approaches.

The last thing I'll say is we talked about CAR T therapy in lymphoma. They are far ahead of us compared to myeloma. In part it's probably the disease itself that, lymphomas tend to respond in a way that's different and more long-lasting than in myeloma. We are not seeing cures right now with myeloma CAR Ts. With that said, we are seeing these unprecedented response rates in patients who have experienced multiple lines of therapy.

I don't use the term game-changer a lot. It is a game-changer in the sense that we are, again, seeing these response rates in patients who normally we may only expect 20 to 30% to respond; and we're seeing 70 to 100% of patients respond. But as the technology improves, we hope to see longer durations of response because that's going to be the key.

Elissa: Absolutely. Now, since we're talking about emerging research, both of you also do research at the University of Chicago. Could you tell us a little bit about current clinical trials that you're now working on for lymphomas and myeloma?

Dr. Riedell: In terms of lymphoma, there's a number of exciting avenues that we're trying to pursue. With CAR T-cell therapy, it's certainly been very impactful in patients with lymphoma. But we're still seeing where a substantial portion of patients that receive that treatment either don't respond initially or don't respond as long as we would like for them to.

And so, there's been some new attempts at improving on that treatment. So, we have a few clinical trials open here that are evaluating different manufacturing platforms. So basically, if we can use different manufacturing techniques in order to improve the quality of those CAR T-cell treatments, that may garner more patients responding and then more patients responding for longer periods of time.

We also have other trials here at the university which are looking at evaluating other cell types that we can essentially turn into cancer-fighting immune cells. So, there's another part of the immune system which are known as NK cells [Natural Killer Cells], and these are a very rare subset of the immune system. And more recently, we've developed some clinical trials and participated in trials which are looking to harness that subset of the immune system; and to turn those into chimeric antigen receptor-bearing cells. And we call those CAR-NK cells.

And so, in the cellular therapy arena, or at least at the University of Chicago where some of our efforts are focused, one of the other areas that I'll just sort of briefly speak about would be in the arena of bispecific antibodies. And these are, I would say in many intents and purposes, very similar to how CAR T-cell therapy works where it's bringing an immune cell towards attacking a cancer cell. CAR T-cells have all that machinery basically inherent with them and are able to independently attack these cancer cells.

Bispecific antibody therapy really is an infusional type of therapy whereby it brings a T-cell, which is a part of the immune system, in close proximity to a cancer cell; and it ends up activating that T-cell and leading to killing of those cancer cells.

And what we've been seeing in multiple subtypes of non-Hodgkin lymphoma now is very high response rates and even, encouragingly, responses in patients who have failed CAR T-cell therapy. And so, this is a really exciting and emerging area of research and one that, that we've been a part of here at the University of Chicago with now multiple trials in our pipeline looking at evaluating these bispecific therapies or BiTE therapies in varying subtypes of lymphoma.

Elissa: Dr. Derman, what about you for myeloma?

Dr. Derman: Yeah, I mean along the same lines, we are really proud of our cellular therapy program; and, along the lines of myeloma, we also have a bispecific antibody that we are investigating in patients even who disease has progressed through CAR T.

We also are still really trying to grow the various number of CAR T products that are out there for myeloma, trying to figure out which ones are going to be the most successful here. So that's another key piece.

For going back to earlier lines of therapy, and in talking about MRD as well, really the pride and joy of our program is something we call MRD2STOP. What this is, is actually trying to do what I mentioned before, just using MRD to figure out how we can guide decision-making.

So, patients who actually have undetectable disease by very sensitive MRD testing in this study would be able to undergo complete discontinuation of their therapy. We are monitoring these patients actually over a three-year period to see what happens; and we'll be conducting MRD tests as well over that three-year period to really define, what happens to the disease when you do that. And so, we're really, really proud of this, to be able to actually stop therapies in some patients who can do so.

For those who are newly diagnosed, that's, obviously, a major area of need. We have several studies that have been ongoing. One of them is that same quadruplet I mentioned of daratumumab and KRd. And this one is actually looking to bypass transplant. So, for patients who may not want to go through with a transplant, but instead would opt for extended therapy with a quadruplet regimen, this is a really exciting option that we're very enthusiastic about.

Elissa: Well, thank you, doctors. That sounds so exciting. Everything you talked about from ASH and then your own clinical trials.

So, on our patient podcast homepage, we have a quote that says, "After diagnosis comes hope." What would each of you say to patients or caregivers listening to give **them hope after a diagnosis of lymphoma or myeloma?**

Dr. Riedell: I would say, in terms of things that I look to, especially with meetings like ASH, is there's a tremendous amount of research in a whole range of cancer

subtypes but specifically in hematologic malignancies. I think I'm astounded each year I get to attend this conference and learn about the new research that's being done, the new molecules that are being developed, and the improved outcomes in patients. And so, I think it's a really exciting time for me as a clinician to be in this space; but certainly, it's really exciting also because there's more therapies that we can provide for patients. We're seeing patients live longer. And also, along that same vein, being able to, in some sense, have more targeted agents for patients and more tailored therapy so it's not just a one-size-fits all. So, I think there's a lot of promise as we get a better understanding of how to use these different agents.

Dr. Derman: And I would echo that. I mean the pace of progress in myeloma specifically is astounding. A lot of my colleagues of a different generation often wondered why I wanted to specialize in myeloma. They couldn't understand it; and that's because we just didn't have great options a long time ago.

It's such a different environment now. In fact, it's so much so that you can't really pin a myeloma doctor down and say, "What is the average life expectancy of a myeloma patient?" because not that long ago people were saying 5 years. Then it was 7 years. Then it's 10 years. And now we don't really know because that number is increasing as time goes on.

So, I think that there's certainly a lot of hope that we can turn this for some into simply a chronic disease that can be managed. And for a significant minority of patients, I really truly think that there are patients who can be cured of this disease, which is traditionally thought to be incurable. The question is figuring out how to identify who those people are and how to be able to take them off of treatment.

Elissa: Well, thank you so much, Dr. Riedell and Dr. Derman, for joining us today and sharing all the exciting updates from ASH and your own clinical trials. Cancer can be a really scary time for people who are newly diagnosed or who have failed therapies, and it's always great to hear about all the latest updates and the new things that are

coming out. And I really think that that gives so much hope to patients and caregivers that are listening, so thank you again so very much for being here with us today.

Dr. Riedell: My pleasure

Dr. Derman: Thanks so much.

Elissa: Also, a special thank you to the University of Chicago Medicine for supporting this episode.

And thank you to everyone listening today. *The Bloodline with LLS* is one part of the mission of The Leukemia & Lymphoma Society to improve the quality of lives of patients and their families. To help us continue to provide the engaging content for all people affected by cancer, we would like to ask you to complete a brief survey that can be found in the show notes or at TheBloodline.org.

This is your opportunity to provide feedback and suggested topics that will help so many people. We would also like to know about you and how we can serve you better. The survey is completely anonymous and no identifying information will be taken.

We hope this podcast helped you today. Stay tuned for more information on the resources that LLS has for you or your loved ones who have been affected by cancer.

Have you or a loved one been affected by blood cancer? LLS 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 LLS.org/PatientSupport.

Highlights from the ASH conference can be found at LLS.org/Blog. You can find more information about lymphoma at LLS.org/Lymphoma or myeloma at LLS.org/Myeloma. All of these links will be in the show notes or at TheBloodline.org. Thank you again for

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