LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Hope in Myeloma: The Road to Long-Term Survival'

Description:

In this episode, we sit down with Dr. Cesar Rodriguez of Mount Sinai Hospital in New York, NY to discuss the evolving landscape of myeloma treatment. Groundbreaking innovations are bringing new hope to patients and caregivers. Dr. Rodriguez breaks down the latest advancements in immunotherapy, including CAR T-cell therapy and bispecific antibodies. Hear how researchers and physicians are working to make myeloma into a manageable, long-term disease, while ultimately searching for a cure.

Transcript:

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

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

Elissa: Today, we will be speaking with Dr. Cesar Rodriguez, an Associate Professor of Medicine at the Icahn School of Medicine at Mount Sinai Hospital and Clinical Director of the Multiple Myeloma Center of Excellence at Mount Sinai in New York City. He focuses on treating patients with plasma cell disorders using early phase clinical trials and novel immunotherapies such as NK- and T-cell redirecting therapies. He has been an active advocate on healthcare disparities and access to cancer care. Aside from his patient care, he is performing experiments studying the biology of myeloma and the effects of different treatment agents as a platform for personalized medicine. Welcome, Dr. Rodriguez.

Cesar Rodriguez, MD: Thank you for having me.

Elissa: So, our episode today is on multiple myeloma. Could you tell our listeners what that is?

Dr. Rodriguez: Sure. Multiple myeloma is a type of blood cancer. It's not a very common type of blood cancer. Approximately 3% of all cancers in adults in the United States are going to be multiple myeloma. And it is a disorder that comes from a type of cell within the blood called plasma cells where these abnormal plasma cells tend to cause some damage to the body, whether it be kidney damage, bone lesions, high calcium, anemia, and frequent infections.

So, to better explain what multiple myeloma is, compare it with a factory and an assembly line. We make more than 300 billion cells of blood each day. So, imagine a factory and an assembly line that's making 300 billion toys. And there's always quality control people along the assembly line, making sure that all the parts of the toys are put in correctly and that the stickers of the toys or the colors match, so that when that product or the toy gets to the end of the assembly line, they can be distributed to the stores, and there's not going to be a kid that's going to be disappointed because their toy's not working well.

The same thing happens with our body. We make so many blood cells that we're bound to make some abnormal cells, and we have some quality control checkpoints that allow the body to identify these abnormal cells and flag them so they can be destroyed. Multiple myeloma is when one of these abnormal plasma cells doesn't get destroyed or flagged by any of these quality control checkpoints and makes it to the end product. So, now we have an abnormal or a mutated plasma cell that looks very much like the healthy plasma cell and has very similar properties. They both produce immunoglobulins that are released into the blood, in the healthy plasma cell, we call it an antibody. But in an abnormal plasma cell or a myeloma cell, we call it an M spike or an M protein because that immunoglobulin that's producing is not a functional immunoglobulin. And a healthy plasma cell, an immunoglobulin or an antibody helps fight infections. But in a myeloma cell, it doesn't do that.

So, then that abnormal plasma cell that made it through the whole assembly line and is now living inside of the bone marrow is going to start to divide. And as it divides, all of the offspring or all the cells that come out of that abnormal cell is going to be producing a similar protein to that initial abnormal cell. And the more of these cells we find in the bone marrow, the higher the concentration of this protein we can detect in the blood. So, that makes the M protein or the M spike go up in the blood; and it actually makes it easy for us to be able to measure and detect this type of cancer based on blood test, and it's a good biomarker. Sometimes, we can detect the whole M spike. Sometimes, we detect fragments of this M spike, which we call free light chains. And there's going to be a very small percentage of patients – I would say less than 3%, that will actually not be producing these proteins or these fragments released to the blood. So, that's a small percentage of patients that we won't have this feature.

But this protein that's floating around can cause damage to the kidney. It can also cause some other side effects because they're not fighting infections, but it could sometimes attack the body in a different way, like autoimmune disorders. Not that frequently, but it could potentially happen.

But then in the bone marrow as these cells divide, it doesn't allow space for healthy cells to grow, so then that leads to anemia. And then it likes to chew into the bone to have more space, which can lead to bone pain and free up calcium from the bone and release it into the blood. And that's how multiple myeloma can cause damage to the body and lead to the problems that we see in myeloma patients.

Elissa: Well, thank you for that great explanation.

Lizette: Now, I know that there's a few related diseases that I'd like to point out. The first one, monoclonal gammopathy of undetermined significance or, as we say, MGUS, as well as smoldering myeloma. So how are these different from multiple myeloma?

Dr. Rodriguez: You bring a very good point, Lizette, because not all of abnormal plasma cells are going to fit criteria for multiple myeloma. There's a whole gamut of disorders related to plasma cells that are from precursor diseases like MGUS and smoldering myeloma to active diseases that are considered active cancer like multiple myeloma and then more aggressive diseases like plasma cell leukemia.

So, to distinguish both, let's talk a little bit about precursor disease, and I like to say precursor disease and compare it to diabetes and prediabetes. When you're a prediabetic, you don't necessarily have diabetes. You're not necessarily on therapy to control your sugar levels; and you're not necessarily already experiencing damage related to diabetes. And the same thing happens with plasma cell disorders. If you're having damage in your body or the abnormal plasma cells are having an impact in your body, then that's considered multiple myeloma or plasma cell leukemia. But anything prior to that, we call that precursor disease.

So, MGUS is abnormal plasma cells in the bone marrow, which is where these cells like to live. But you don't have any end organ damage. You don't see any signs of kidney damage, no anemia, no high calcium, no bone lesions, but you do have a detectable protein in the blood that's produced by plasma cells or the myeloma cells. But M protein, which is the protein that's produced by these cells, is less than 3 grams per deciliter. You have less than 10% involvement of the bone marrow with these abnormal plasma cells, and these patients can eventually evolve to multiple myeloma with time, but the risk is low. It's just 1% each year.

The second precursor disease is the smoldering myeloma, which is one step ahead, but not quite multiple myeloma yet. And the distinguishing feature of smoldering myeloma is you will have abnormal plasma cells in the bone marrow or myeloma cells, and the range of involvement is between 10 and 60%. It's less than 60%, but 10% or more.

And in addition to that, you cannot have any evidence of organ damage, whether it be kidney damage, anemia, high calcium, or bone lesions. And we distinguish MGUS and

smoldering myeloma because smoldering myeloma has a higher risk of transforming into active multiple myeloma and requiring therapy. And we divide the smoldering myeloma based on the risk of it evolving to active myeloma based on certain characteristics, whether they have mutations that make it high risk, the amount of marrow that's involved, and the amount of measurable protein or free light chains, which are the fragments of this protein that we can detect in the blood.

Elissa: So, sometimes myeloma patients also have a diagnosis called amyloidosis. What is that, and why do patients also have that secondary diagnosis?

Dr. Rodriguez: Amyloidosis is like the cousin of multiple myeloma. They come from the same family. And when we talk about amyloidosis in this set, I want to just clarify that it's AL amyloidosis, because there's different types of amyloidosis. There's AA, there's ATTR, and then there's a very small percentage of amyloidoses that are triggered by other chronic inflammations or other diseases. But when we talk about AL amyloidosis, this is a cousin of multiple myeloma and all of the precursor diseases because it comes from the plasma cell. A plasma cell that, just like the myeloma cell, is producing an abnormal immunoglobulin.

The thing that distinguishes amyloidosis from regular myeloma or MGUS or smoldering myeloma is that the way that this immunoglobulin is produced, it's folded differently. So, once it's released out into the blood, it's a protein that normally doesn't float in the blood like the normal immunoglobulins. It's actually sticky, and this stickiness makes it want to attach to different parts of the body, whether it be the heart, the kidney, the gut, the bone marrow, the nerves, soft tissue, and the lung. And as these sticky proteins build up in that tissue, it causes inflammation which can then cause scarring and damage to that organ. And that is the reason why amyloidosis can cause heart failure, or kidney failure, or neuropathy, autonomic dysfunction, diarrhea that's uncontrolled, problems with breathing, or inability to have space in the bone marrow to make proper blood without having a packed marrow with abnormal cells.

So, distinguishing amyloidosis from myeloma is, one, the protein that's being produced. One of them is sticky and tends to cause inflammation wherever it sticks. In myeloma, we don't have that feature. But because these proteins are sticky, you need a very small amount of these to actually cause symptoms and damage. So, a lot of the times in AL amyloidosis, when we do a bone marrow biopsy to look for these abnormal plasma cells, we tend to see a smaller percentage of these cells because even though there's a smaller amount of cells and a smaller amount of protein produced by these abnormal cells, the stickiness causes more damage in the organs in our body compared to the M spike or the free light chains produced by myeloma cells or smoldering myeloma or MGUS.

There is an overlap at times, and sometimes you can have multiple myeloma and have AL amyloidosis, and that tends to be less than 20% of the cases, but it can happen at any time point of the disease. And there could be occasions where somebody is diagnosed with AL amyloidosis and can eventually transform to multiple myeloma, and there's an overlap there as well. So, that's why I say they're like cousins because they're related. They come from the same cell type, the plasma cell. It's just the different features and characteristics of the proteins that they produce that are going to give us different clinical picture between one and the other. But the treatment is very similar between the both, and when we talk about AL amyloidosis, the treatments that we're using for AL amyloidosis come from what we've learned how to treat multiple myeloma.

Lizette: And you mentioned how you diagnose when somebody has myeloma. Is that the same way, the same testing to find the amyloidosis?

Dr. Rodriguez: It's similar, but it has its unique features. And in multiple myeloma, we tend to see kidney damage, anemia, high calcium, or bone lesions, and frequent infections. In AL amyloidosis, because it can deposit in the heart, the kidney, or the gut, depending on what organ it's causing damage is what we could potentially see initially. So, it's more common to see heart failure in these patients or significant

kidney damage, despite having just a small amount of abnormal protein detected in the blood or in a small M spike or a small amount of free light chains. But then amyloid patients will also have, at times, neuropathy that is unexplained or might have diarrhea that is unexplained.

So, in addition to doing the myeloma panel that looks for an M spike and looks for free light chains and immunoglobulins, we add other studies, depending on what organ we think is involved. We might need to do cardiac studies, or we might need to do colonoscopies and take biopsies if we think that there is gut involvement causing diarrhea or causing uncontrolled nausea. And at times, we might need to do some nerve conduction studies and even biopsies, and a fat pad biopsy if we think that this protein might be depositing in nerves or in the soft tissue or other body parts. So, it's the same myeloma test, but then we build up on that, depending on what organ we think is involved and that helps with the diagnosis.

Lizette: Sure. And I know that over the years the different testing to get a definitive diagnosis of myeloma has kind of evolved. I know that when I started, it was a urine test; and I believe that at this point there's different testing to get that definitive diagnosis of myeloma?

Dr. Rodriguez: Correct. I don't want to call you out on age or anything, but yes. When I was training, we would do blood tests to look for an M spike by serum protein electrophoresis and immunofixation. We would do quantitative immunoglobulins, but we didn't have access to serum free light chains (sFLC) until the last 15-20 years. Before that, we relied on a 24-hour urine collection to look for Bence-Jones proteins. Now, we have access to serum free light chains, and we've noticed that a lot of those patients with multiple myeloma that we detected only by Bence-Jones proteins in the urine, we're picking them up by doing the serum free light chains in the blood.

So, in my patients, and I think in a lot of institutions, the serum free light chains have replaced the 24-hour urine collection because it's much simpler. It's a hassle to be

collecting urine for 24 hours and then bringing the jar for studies. But there are special occasions where we might still need to do this 24-hour urine collection if the serum free light chains and the SPEP (Serum Protein Electrophoresis) do not show anything and we still have a suspicion that there might be some plasma cell disorder in these patients or if we want to confirm that these patients are truly in a complete remission.

Lizette: Yeah. And you mentioned that there are some signs and symptoms that are similar to other diagnoses. What usually brings somebody to the doctor that has myeloma?

Dr. Rodriguez: Myeloma is one of those tricky diseases that has very vague and nonspecific symptoms. Pain, and it tends to be lower back pain as a common symptom from this disease. And if you think about it, on average, the patient who is diagnosed with multiple myeloma is 68, 69 years of age. So, naturally, there's going to be many other reasons for back pain; and that's one of the reasons why the diagnosis of myeloma sometimes gets delayed because we're managing just back pain because of aging or because we don't have strong muscles in our core that could be leading to that or just we blame it on arthritis or just wear and tear. But that's a common symptom that can happen. And a lot of the times, an uncontrolled pain tends to be a reason to do studies by the primary care doctor or by an orthopedic doctor if they actually broke a bone, which is another way that we can diagnose myeloma.

But then, we do get a lot of referrals from the primary care doctor or the kidney specialist because somebody has kidney damage, has renal failure without a clear explanation. They have renal failure without uncontrolled diabetes or without uncontrolled hypertension, or they have anemia without a clear explanation. Their iron stores are good, their B12 and folic acid levels are normal, but they still have some degree of anemia, or because they have an elevated protein in the blood, but their albumin level is lower than normal and that gap between the total protein and the albumin is different.

So, a lot of the ways that we pick up on myeloma can be picked up with annual checkup because the symptoms are very vague. It's just feeling tired, having pain, back pain or bone pain. And these vague symptoms, a lot of the times get misdiagnosed for a period of time and are just given pain medications or tell the patients to exercise or lose weight or something like that.

Elissa: So, could you tell us a little bit about the staging and the risk level of myeloma?

Dr. Rodriguez: Sure. When we think of cancer, the first thing that people think of or want to know is, how advanced is this disease and what stage is this? We're so used to talking about solid tumors and cancer that affects organs that we are kind of familiar with if it's early stage, it's curable. If it's late stage, it means that it's spread over the body; and it might not be curable.

But when it comes to multiple myeloma, this is a little bit different. We do have staging system. We have a Stage I, II, and III. But this is more for research purposes, and it might help us a little bit with some prognostic factors, but it's not really going to change the treatment.

Elissa: Okay.

Dr. Rodriguez: And it's not going to help us determine if this is early on or late stage because, if you think about it, multiple myeloma is a blood cancer; and blood is all over the body. So, from the beginning, it's already all over the body.

Elissa: Right.

Dr. Rodriguez: It's not like solid tumors or breast cancer or lung cancer that when somebody hears Stage III, Stage IV, you're already thinking, oh, it's metastasized, or it's already spread all over.

So, for practical purposes, I would say that there is a staging system for myeloma, the Revised International Staging System (R-ISS), which we use as Stage I, II, and III. But it's more for research purposes and kind of get a better sense as to what we want to do down the line. But it doesn't impact the therapies that we use as much. It just helps us get a sense of how likely we're going to be dealing with earlier relapses or is there going to be a probability that this type of cancer might be a little bit more resistant to the therapy that we're using?

Elissa: So, are there different risk levels as well? So, lower risk, higher risk? Maybe one might be more aggressive?

Dr. Rodriguez: So, a Stage III would be the most, I guess, aggressive I would say, if we're going to use a word, although I don't want to use that word necessarily. But, in terms of risk factors, I would say Stage III has higher risk factors or is more troublesome because the Stage III means that there's some mutations that make this disease more likely to cause a relapse or more likely to not respond completely to the treatment that we're giving. A Stage III also might meet the criteria of Stage III because of how quickly this cancer is growing.

So, just to give an example, the staging system is measured or determined by a few things, by albumin, which is a protein in our body; by beta-2 microglobulin that helps us as a marker of how cells are growing and inflammation; and then mutations that these cells have, the myeloma cells, and then LDH. Those are the main criteria that are factors that we use to stage.

So, Stage I is a very, I would say, good prognostic factor. Meaning that Stage I patients who respond to treatment tend to stay in remission for a longer period of time, and it's easier to handle versus a Stage III. But having said that, these are just statistics, and you could have aggressive mutations and still behave like a very mild myeloma that's very easy to control. And you could have a Stage I, which technically

would be very easy to control and behave very aggressively, and that's what we call a functional high-risk disease.

So, it's one of those things where I would say it's good to know if you want to know what your stage is. It's not something that you should focus too much on. It's more for the scientists who are doing clinical trials that you try to understand the risk of a relapse or responding to certain drugs. And in some locations, if there's a lot of aggressive mutations, then in those cases we might change the therapy, regardless of whether they're a Stage III or a Stage II. So, the mutations, I think, is something that gives us more information; and high-risk cytogenetics is something that I would consider more important in terms of what therapy I'm going to give to this patient.

Lizette: Yeah, so mentioning therapy, I'm going to date myself now and say that over the past 16 years I've seen such incredible movement with the therapies for myeloma and such different therapies for folks, as well as therapies that are not just causing better outcomes but also attributing to patients' quality of life. So, can you go into the current treatments for myeloma?

Dr. Rodriguez: Sure. So, I'm going to date myself too a little bit, although not too much, but when I was in training, we didn't have any of these monoclonal antibodies or novel immunotherapies that we're using a lot nowadays. We used to use what we called back then novel therapies, which would be proteosome inhibitors like bortezomib, carfilzomib, ixazomib; and would also use immune modulators like lenalidomide, pomalidomide, and to a certain point thalidomide, although we don't use that much any more.

But then in the last ten years, we've had an explosion of new therapies that have become available. In 2015, we had the first monoclonal antibodies approved for myeloma. So, we have now daratumumab and isatuximab that targets CD38; and then we have elotuzumab that targets SLAMF7 (Signaling Lymphocytic Activation Molecule Family 7). And then we had selinexor approved also afterwards, which is a

nuclear export inhibitor which we use also in combination with other drugs. And then more recently, in the last five years, we've had the novel immunotherapies, which are bispecific T-cell engagers such as teclistamab, talquetamab, and elranatamab, and CAR T therapy such as ide-cel and cilta-cel. So, in the last five years, I'm going to say that it's where we've had the biggest change in our whole concept of how we treat multiple myeloma and our expectations of the therapies.

Before these novel immunotherapies, the bispecifics and CAR T therapies, we were very used to using combination therapy. And we would combine three drugs to try to give optimal responses, and we would take a drug from each class, whether it be a proteosome inhibitor, an immune modulator, a monoclonal antibody, steroids, or an alkylator like cyclophosphamide or melphalan or one of those old school drugs that we still use because they're oldies but goodies, and we would expect with new therapies a response about 30% in people who have had multiple relapses. Now with these novel immunotherapies, as single agents, we're seeing responses that range between 60 and 97% as a single drug, which is really blowing it out of the park, and it's really changing our whole paradigm of doing combination therapies and then, our expectations of how effective these therapies could be in people who have had multiple relapses or who are heavily pretreated.

So, an example, we have the bispecifics, the teclistamab, talquetamab, and elranatamab. As a single agent, response rates range between 60 and 72%. And with CAR Ts, such as cilta-cel and ide-cel, we're seeing responses that range between 86 and 98%. And these are all in patients who received at least four prior lines of therapy.

So, that's what led to the FDA approval of these agents; and now we're doing clinical trials trying to see if we can use these therapies earlier, whether it be at first relapse or even at first diagnosis and see if we can incorporate the bispecifics to newly diagnosed patients or if we can incorporate CAR T instead of a stem cell transplant or in those

who are transplant ineligible do a CAR T and then see how to sequence these therapies.

So, our paradigms have changed significantly from multiple myeloma being one of these cancers that would be terminal and we would have an expected course of approximately three to five years to now a chronic disease. And I go again to the diabetes concept. You can live with diabetes as long as it's controlled, and with either pills and diet. And if you get sick or you eat too much cake and it gets out of control, you might need some extra insulin until it gets controlled again. But as long as your disease is controlled, you can live a good life.

And the same thing happens with myeloma now with all of these new therapies. As long as we can control the disease, then you can live with the myeloma and have as normal life as possible and live a normal lifespan. We're not using the word cure yet-

Lizette: Okay.

Dr. Rodriguez: -because these agents are still too new, and they've only been approved in the last five years, and we definitely want to make sure that somebody stays in remission for more than ten years. We say the word "functional cure" now because we have patients who are off therapy and have been in remission for more than five years. But I think that we're still in the early phases of these immunotherapies, and we're learning how to use them better if we need to combine them with other agents to make them more effective, or if we need to come up with newer generations of these immunotherapies, just like we did when proteosome inhibitors and immune modulators started to come up and then newer generations of these agents came out.

Lizette: Sure. And I know that I was always told that myeloma is a chronic type of blood cancer, meaning that it tends to come back. So, with these newer therapies, we're really looking towards the future for hopefully cure, but is the goal of treatment right now still the same, which is really trying to get longer periods of remission?

Dr. Rodriguez: The goal is always going to be to contain the disease. But there's two main things that we need to keep in mind when we're treating a patient with multiple myeloma. Is our final goal quality of life, or is our final goal trying to achieve remission and possibly a cure? Because that's going to depend also on how aggressive we are going to be with the therapies that we give. If we're trying to achieve a cure or a remission and a durable remission, then we need to focus on agents that are going to be probably more aggressive, but at the same time well-tolerated by the patients who are receiving the therapy.

In somebody who might be very frail or who might be in their late 70s or 80s, and we know that the therapies that we have already can contain the disease on average by eight years, do we need to be that aggressive? And those are the questions that we tend to ask when somebody either is diagnosed with myeloma for the first time and we're offering a therapy for them, or they're relapsing and we're trying to offer a salvage therapy for them.

Now having said that, this is a concept of quality of life and really like throwing the sink at the patient in somebody who we're trying to achieve a potential cure or a durable remission. But this concept is also changing. Why? Because CAR T and bispecifics have shown to be very well-tolerated, even in elder patients. So then at what points do you say they're not eligible for one or the other and is this going to be too much for that patient? So, that's also something that's being questioned now in terms of who is considered too frail to receive these therapies, and should patients who are in their late 70s or 80s be receiving CAR T or be receiving bispecifics?

Elissa: So, when you talked about the "functional cure," was that really related to CAR T-cell therapy and bispecifics?

Dr. Rodriguez: We've seen functional cure with other therapies as well. We've had some patients that get induction therapy with what we call now the standard of care VRd or dara-VRd and then get a transplant and then they go on maintenance, and

they stay in remission for three, four, five years on maintenance. And then we stop the maintenance and they remain in remission for another five, ten years; and they're doing great. It's a small percentage of patients, about 10 to 15% of the patients will have these well-controlled diseases. And some of them will die of something else and their myeloma never comes back. But this is a small percentage of patients.

Now that we're playing with CAR T and bispecifics, we think that we're actually going to move the needle up and have a larger percentage of patients that are going to have controlled disease without a relapse down the road. But it's still too early to say that with certainty. We know that these therapies are improving what we call progression-free survival and overall survival, so we're having better control of the disease; and it's also impacting outcomes and the patient's ability to stay alive. But we don't know what percentage of the patients are going to have these "functional cure" that, where they're going to be off therapy for five, ten years and to not relapse.

Elissa: So, you mentioned that some patients were getting a transplant. Now that is autologous, right? So, using their own cells rather than using donor cells?

Dr. Rodriguez: Correct. When it comes to multiple myeloma, transplant has been a big part of our initial therapy. When somebody has a new diagnosis of myeloma, we tend to do a three-step approach. We do several cycles of induction therapy to try to contain and control the disease, and then, we do a second step which is consolidation; and it tends to be either a stem cell transplant or additional chemotherapy for those who are not eligible for transplant.

And this stem cell transplant tends to be an autologous transplant. There's two main types of transplants, autologous transplant and allogeneic transplant. Allogeneic transplant is using another person's bone marrow, and those tend to be used more in leukemia or lymphomas and other types of blood cancer. But for multiple myeloma, an autologous stem cell transplant is very effective at doing a deep clean of the bone marrow, of any lingering cancer cells by the therapy that we give with the transplant.

So I want to just clarify there, that the treatment of the stem cell transplant or the autologous stem cell transplant, the transplant is not the treatment itself. It's the chemotherapy that we give right before the transplant that's actually doing the work and helps us contain the disease better.

So, to this date, we still are doing stem cell transplant in patients. People who have high-risk disease, people who still have uncontrolled disease after completing their induction would benefit from autologous stem cell transplant. We are now starting to offer patients who have standard-risk disease, don't have high-risk cytogenetics or high-risk disease and have controlled disease the option of collecting the stem cells and not necessarily doing a transplant at that point but leaving it for a relapse. And that's something that's starting to gain some more traction because we're having such well-controlled disease with the combinations that we're using as part of the induction and as part of maintenance.

Now, currently, we're trying to study if CAR T or bispecifics could potentially replace transplant and have a better response down the line and not have to need maintenance or give them a possible cure or a functional cure.

Elissa: Okay, now you discussed being able to tolerate the treatment. What are the side effects that come with these various treatments, and can they be managed?

Dr. Rodriguez: When we're talking about these new novel immunotherapies like bispecifics and CAR T, the main side effects of both classes of drugs are what we call CRS, or cytokine release syndrome, which this tends to be fever. And the fever could be pretty severe, or it could be mild fever. And it can be accompanied with low blood pressure or low oxygen levels. These complications are measured by a grading, and about 70% of the patients are going to develop some type of CRS in these two classes, but a small percentage of patients will get to the point that they need oxygen or that they need medication to help with the blood pressure.

As we have more experience with these agents, we're learning how to control this CRS or even prevent it. And from when we started, I'm going to say almost eight years ago or ten years ago playing with bispecifics and CAR T, we've come a long way. And now, we have medicines that help prevent the CRS, like tocilizumab or dexamethasone. And then, we also have therapies to treat it early and prevent it from getting worse, like the tocilizumab and the dexamethasone.

Another side effect that we're seeing with this two classes of drugs is neurologic toxicities – headaches, confusion, tremors. It's more common in CAR T than bispecifics, but it can present in both. And we have therapies to treat that like dexamethasone and anakinra. We've learned who is at higher risk of developing these side effects. And then, we've also learned that in CAR T in particular, there's some additional neurologic side effects that we're seeing in a smaller percentage of patients, like what we call Parkinson-like movements or delayed neurologic toxicities with memory.

Those are the two main side effects that we're seeing with CAR T and bispecifics that we hadn't seen with other drugs that we used for multiple myeloma. And just like with any chemotherapy, people can have a risk of developing an infection, whether it be bacterial or viral or potentially fungal infection. But these are things that we're seeing with these two classes of drugs as well.

So, when we're deciding on how to treat a patient, we need to keep in mind, is the patient already having signs of Alzheimer's or has history of strokes or have had some, cognitive impairment or mental limitations that, if they get CAR T, could put them at higher risk of Parkinson-like movements or neurologic toxicities? Or is this a patient that has lung problems and emphysema and frequent respiratory infections? Do we want to use one of these BCMA-directed agents, whether it be CAR T or bispecific? Or do we want to use another target called GPRC5D (G Protein-Coupled Receptor Class C Group 5 Member D), which we have in bispecifics, and we're studying in CAR T?

So, there's different things that are going to be factored into the equation to determine what might be suitable for these patients. But overall, I would say that both of these classes of drugs, the bispecifics and CAR T are pretty well-tolerated; and we've been giving it in patients, even in their early 80s. It all depends on how functional they are.

Elissa: Right.

Dr. Rodriguez: Age is just a number.

Elissa: I like to hear that. Age is just a number.

Now, I want to discuss a couple of side effects related to the bone. The first is bone pain. Now, is that an effect of the disease or as a result of the treatment or both?

Dr. Rodriguez: I'm going to blame it a little bit on both. So, there are patients who are getting bispecifics or CAR T that develop bone pain when they start getting the treatment and we call this a tumor flare. And it doesn't necessarily need to be the bone. It could be also if somebody has a plasmacytoma or, or a tumor from myeloma cells. But any area that has a high concentration of myeloma cells, because the way these therapies work is activate the immune system, so that the immune system go and attack those cancer cells, then you're going to cause inflammation in that area. And if it's in the bone, it can cause increased pressure in that area because you're attracting more cells to that area. Or if it's a tumor, a plasmacytoma, it can cause that tumor to grow temporarily because it's being penetrated or infiltrated by these inflammatory cells.

And these inflammatory cells that are part of the immune system are causing heat in that area so that they can attract more cells to help fight those myeloma cells. That can transiently cause what we call a tumor flare and can cause transient pain if you have a big bone lesion or if we have a plasmacytoma or if there's a lot of myeloma in the marrow.

And the way we treat this is by giving steroids. Dexamethasone has been a great agent that helps reduce that inflammation so then, it controls the pain significantly. And we normally tend to see these bone pain or tumor flares when we're doing the step-up portion of bispecifics or very early when we give the CAR T. We don't see these down the road.

Elissa: Okay. Now, the second one that I want to bring up is osteonecrosis of the jaw. What is this, and why does it happen?

Dr. Rodriguez: So, osteonecrosis of the jaw, and the name says it, but I'm going to simplify it. It's that there's a complication where some parts of the jaw or the mandible, but mainly the jaw, the bone doesn't get enough blood; and that part of the bone tends to die.

And this is a complication that we see associated to bisphosphonates, whether it be zoledronic acid or denosumab, which we tend to use a lot in multiple myeloma because it helps strengthen the bones, and it also causes synergy with the therapies that we give to treat multiple myeloma. Just a small percentage of these patients, less than 10%, that might develop this osteonecrosis of the jaw, which the way you can detect is you might start having some jaw pain or you could see part of the bone showing through the gums and not healing. So, at times it looks like an infection, or it looks like there's a little bit of an exposed bone there that may be painful at times. And it doesn't tend to heal and that's because that little part of the bone is not getting enough blood and its gradually kind of chipping off and coming out.

So, in a situation like that, what we tend to do is we tend to have a dentist, or an oral surgeon help us by doing some cleaning in the area. There's an infection or if there's a bone sticking out to help clean it and then do mild rinses and let the body gradually heal. It does heal. It might take time. Sometimes it could get infected, sometimes it could be tender, but it tends to heal with time.

And in a case like that, while the patient has osteonecrosis of the jaw, we hold off on the bisphosphonates. But that doesn't mean that they cannot get it in the future. Once it's completely healed, you could potentially retry giving this to help strengthen the bones if somebody has osteoporosis or osteopenia that would benefit from a bone strengthener.

There are a few things that can predispose to osteonecrosis of the jaw, and that is people who have poor dentition, people who have already some infection or abscess in their mouth, in the gums, people who are getting extractions while on this medications can also have a risk of developing osteonecrosis or any type of manipulation in the jaw bones.

Fillers don't tend to cause this risk. Root canals don't tend to cause this risk. So, that's why before we start these therapies, we tend to have the patient go see a dentist and get cleared in case they do need to have their teeth pulled or bridges done or things like that, they can do it before we start the therapy. And then, if they need to get it done while they're on therapy, we hold the therapy for a few months so that they can have the procedure done without an increased risk of osteonecrosis of the jaw.

Lizette: Thank you. And I know that we've been speaking about the greatest and the latest therapies. But are there any emerging therapies or those that are currently in clinical trials that you're particularly excited about right now?

Dr. Rodriguez: Yes, we do have new bispecific T-cell engagers. We have new CAR T therapies that are being studied. We're also playing with NK cells with the same concept of trying to activate the immune system without causing so many side effects. And then. We're also doing targeted therapy, where we're targeting certain genes that are overexpressed in certain cancers to see if that can help control or treat the myeloma better.

There's this idea of personalized medicine where we take into account not just the fact that you have myeloma, but what mutations does your myeloma have, and what could it be susceptible to? And there's a lot of studies that we're doing now precisely on trying to personalize the treatment for each individual because multiple myeloma, like the name says, can present in multiple ways and has many levels of aggressiveness.

So, currently, for example, I have a study called Precision Medicine that can help identify potential features that the myeloma has that can determine if certain drugs or certain therapies that might be for myeloma or for other cancers could potentially be used to treat multiple myeloma more effectively.

Elissa: That's great. So, our final question today, Dr. Rodriguez, on our patient podcast home page, we have a quote that says, "After diagnosis comes hope." What would you say to patients and their loved ones to give them hope after a diagnosis of myeloma?

Dr. Rodriguez: I think it's a very appropriate phrase and quote because now more than ever do I have hope that we are going to reach a cure, and we're going to find a cure. And the fact that every year we're having at least one new drug approved to treat multiple myeloma and the responses that we're seeing with these new drugs is just completely mind-boggling. So, I am confident that we are going to reach a cure in the near future or if we don't cure it, at least reach a therapy that's going to help contain the disease for good and be easy to tolerate so that whoever has it can live a normal life and just say, "Oh, I have myeloma just like I have cholesterol."

Elissa: That's wonderful. What I love is that you talked about myeloma really being able to be a chronic disease. So, while you are looking for that cure, patients are staying alive. They're having, hopefully, a better quality of life, and they're being able to maintain that progression-free survival. So, that's wonderful.

Well, thank you so much, Dr. Rodriguez, for joining us today and talking all about myeloma. I'm sure you've given so much hope to patients and their families that are listening right now, and we really appreciate you joining us.

Dr. Rodriguez: It's a pleasure talking to you both.

Elissa: Thank you.

Lizette: Thank you.

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

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