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The Bloodline with Blood Cancer United Podcast

A Podcast for Patients and Caregivers

Episode: 'Facing Multiple Myeloma: A Guide to Choices, Care, and Confidence'

Description:

Multiple myeloma can feel unfamiliar and overwhelming at first, but today's advances tell a much brighter story.

In this episode, Dr. Andrew Yee of Massachusetts General Hospital explains what myeloma is, how it's diagnosed, and why new treatment options, from four-drug regimens to CAR T-cell therapy and bispecific antibodies, are transforming patient outcomes. With enthusiasm and relatable analogies, he highlights how patients may progress from periods of significant challenges to reaching a level of stability and well-being that allows them to live fully. This conversation offers clarity, confidence, and real optimism for anyone navigating myeloma.

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. Andrew Yee, the Clinical Director of the Center for Multiple Myeloma at Massachusetts General Hospital, Brigham Cancer Institute and an Assistant Professor of Medicine at Harvard Medical School. He is actively involved in clinical trials in multiple myeloma, where he leads several investigatorinitiated trials and serves as a principal investigator on a range of multicenter trials. Welcome, Dr. Yee.

Andrew Yee, MD: Well, thank you very much for having me today and for giving me an opportunity to talk about multiple myeloma. I really appreciate this.

Elissa: Well, thank you for being here. We're excited about this conversation. So, our episode today is on multiple myeloma. Could you explain to our listeners what that is?

Dr. Yee: Right, so, I think many listeners, when they hear the word "multiple myeloma," this is the first time they're hearing it. It's because people first hear myeloma. Then they think is it melanoma, right? But it's not. That's a really common thing. So, multiple myeloma is a type of blood cancer.

So, myeloma is a cancer of plasma cells, which is a type of white blood cell that lives in the bone marrow. And when I discuss this with patients, I talk about how, any cell in the body can become cancerous. Like lung cells can become lung cancer. Breast cells can become breast cancer. But when a white blood cell becomes cancerous, it really depends on what kind of white blood cell it is.

So, some white blood cells, if they become cancerous, we call that leukemia. Other types of white blood cells, if they become cancerous, we call it lymphoma. But then there's a very special type of white blood cell called the plasma cell; and if it becomes cancerous, we call it multiple myeloma.

Now, what distinguishes multiple myeloma from other types of blood cancers is it has a range of manifestations. I think about these plasma cells as a special type of white blood cell and it lives in the bone marrow, primarily. That's where its normal home is. And when I think about the bone marrow, I try to use this analogy like a cannoli. So, when people think about bones, they think about the hard shell of the cannoli. But there's also the cannoli filling; and the cannoli filling's the bone marrow, and the bone marrow is the factory that makes your red blood cells, your white blood cells, and platelets. And the plasma cells share the space with the factory that makes your blood.

And the plasma cells' job in life is to make antibodies to protect you from infection. So, the plasma cells are part of the immune system; and these antibodies that they make are proteins which bind to bacteria, and they bind to viruses. So, if you get a flu shot or if you get a pneumonia vaccine, your body makes antibodies to those viruses or bacteria; and they're made by plasma cells.

So, let's go back to the cannoli analogy. If these cells become cancerous, they can thin the shell of the cannoli. They can involve the bone. So, patients with myeloma having a symptom related to the bone, such as a compression fracture, breaking a bone, bone pain is a common manifestation. These cells live within the factory that makes their blood. If patients have myeloma, they can have low blood counts; and low blood counts can be associated with fatigue.

The antibodies that these cells make, if these plasma cells become cancerous, sometimes it can make so much protein that they can clog up the kidney; and it can cause kidney dysfunction. And then, finally, you think about the cannoli shell, the bones as being calcium. So, if it thins the cannoli shell too much, that extra calcium can be elevated; and that can also be another manifestation of multiple myeloma.

So, just to put things in context, it is a blood cancer. And the reason why many people haven't heard of it, it's not very common. Breast cancer's very common. Maybe about 300,000 women are diagnosed a year in the US with breast cancer; and lung cancer, maybe 250,000. I haven't had a chance to consult these numbers from a table. So, these are just approximations.

But then myeloma is about 35,000 cases a year, so it's not as common. And the median age of diagnosis is 69; so this is a cancer that tends to affect older people. And I think something I want to impress upon to listeners is that this is a type of cancer that's very treatable. It's not curable, but it's very treatable. And the majority of patients do very well for extended periods of time.

So, when people start looking this up online, they read about all this stuff; and they get kind of panicked, which I understand. But the numbers you see online are already out of date in terms of how people do. So, when I tell patients that the majority of patients do fine and that they can go back to the quality of life that they had before they were diagnosed. But, of course, nobody wants to be diagnosed with cancer.

When I meet with somebody, hey're at their lowest. They just heard about this diagnosis; they never heard about it before. But, I feel fortunate to be in a position where there's hope and that these patients can do better and they can succeed, and they can feel great. So, that's what I try to bring to the conversation.

Elissa: Wonderful.

Lizette: Yeah. So, you're saying that myeloma is really a type of chronic cancer, right? So, is the goal for treatment management of symptoms and not really cure at this point?

Dr. Yee: Yeah. Right. At the time that we're recording this, it's not considered curable. And so, the reason why we do treatment is to help patients live longer and live better. So, if patients have symptoms, like say their bone hurts or they're fatigued, or their kidneys don't work as well, the goal of the treatment is to help them recover the organ function as well as help them feel better. It's to help those symptoms. So, that's priority number one.

And then baked into that is that with treatment, patients live longer, as well. When I see a patient for the first time, this is like front and center. This is what they're thinking about 24/7. And that's totally understandable. And the hope is that once they get treatment underway like a year from now, what goes from being on the front burner is on the back burner. They're not thinking about it all the time and that they can just move on with their lives. So, majority of patients, that's the case.

Yes, there are smaller percentage of patients where the road can be quite bumpy. And so, we do our best to try to make that road as smooth as possible.

Lizette: Okay. And I know that some patients have MGUS, which is a monoclonal gammopathy of undetermined significance. Is that related to myeloma?

Dr. Yee: Yeah. This is another condition that we see very frequently as well. And monoclonal gammopathy of undetermined significance is a precursor condition to multiple myeloma. We've talked about the plasma cells that live in the bone marrow; and if they go bad and they become cancerous, they can cause all sorts of problems, right? They can thin the cannoli shell. The antibodies, the excess, they can clog up the kidney. So, we think about myeloma as causing all of those potential problems.

In monoclonal gammopathy of undetermined significance, you have the same plasma cell; and it's mainly overactive, but it's not causing any damage. That's been the traditional definition; and we can get onto a more nuanced definition maybe potentially when we think about smoldering multiple myeloma, which is another topic.

This is a precursor condition; and it turns out that about 3% of people over the age of 50 actually have this precursor condition. It's an asymptomatic condition, and it does not have any symptoms. But the way these patients are diagnosed is that they have some bloodwork that's done, and it shows this abnormality.

And this bloodwork consists of looking for this extra protein. So, you can do a specialized blood test called the serum protein electrophoresis and include immunofixation, serum-free light chains. You can do these specialized blood tests to actually look at the output of these plasma cells.

Now, it's not part of routine primary care to get this tested for. So, if you see your primary care doctor he or she will check your cholesterol, check your blood count. These are all routine tests. But in some situations, you may go to see the doctor with a problem, like maybe your blood count might be a little bit low or maybe your kidney function might be off a little bit; and then that might prompt further investigation, and that leads to this extra special test done.

So, just having this precursor, does that mean you're guaranteed to have myeloma? It turns out that only 1% of people who have this condition per year will develop myeloma. So, in 20 years, it might be about 5 or 10%.

So, a common scenario is this bloodwork gets tested; and then they see this abnormality in the blood; and they start Googling it. And the first thing that pops up is multiple myeloma, and then they hear they have this blood cancer.

Elissa: Yeah.

Dr. Yee: And so, the first order of business is to say, "No, you do not have myeloma. You have a precursor condition."

So, just taking these analogies further. I think about like a car. And if you buy a brand-new car and you look under the hood and you look underneath the car, you're not going to find anything wrong with the car because it's brand new, right? But if you have a car and you've been driving it around, say it's like five years old, ten years old. We live in Boston and there's a lot of salt on the road. Okay, so if you look under the undercarriage of the car, do you expect a ten-year-old car that has 100,000 miles on it to look completely pristine, no, you expect there might be some wear and tear that you expect to see; and you might expect to see maybe a little bit of rust. That's expected.

And so that could be another way of thinking about this would be this is a condition that, as you get older the likelihood that you may have it gets higher. You sometimes will see things that may or may not affect the function of the car. So, if you see a little bit of rust underneath the car, you kind of just accept that, "Oh, it's an older car." You wouldn't expect that in a newer car in the same way, this wouldn't be something a pediatrician would encounter, right, because it's just not something seen in kids. But as you get older, you're not going to expect them to all work perfectly.

Now, where this gets complicated is that you have some rust; and then over time that rust can accumulate. If that rust is starting to affect the function of the car, then it becomes something you would take very seriously, right? If it's starting to affect the brakes, well then you've got to treat it, right? So, that's kind of the distinction between, MGUS and multiple myelomas when the rust actually affects the function of the car, if it affects the brakes, the transmission, then, that's affecting the function of the car. And that's when you would treat that. So that's kind of the distinction; but it's kind of a complicated distinction.

Lizette: Okay. I know that you just mentioned smoldering myeloma.

Dr. Yee: Yes. So, smoldering multiple myeloma is sort of an area between a little bit of rust and when the rust actually affects the function of the car.

Lizette: Okay.

Dr. Yee: And so smoldering multiple myeloma is defined, there's no end organ involvement. Patients have normal blood counts. There's no bone involvement. But if you want to do a bone marrow biopsy, there's over 10% plasma cells in the bone marrow. Normally, 5 percent's normal on average. But if it's over 10% involvement, then we consider it, by definition, smoldering multiple myeloma, at least. Or if the amount of monoclonal proteins like 3 grams per deciliter the amount of extra protein, you can measure it. And then if it's over 3 grams, then we call it smoldering by definition.

So, if it's over 10% plasma cells, then your risk of it becoming active myelomas higher. So, it goes from a condition from 1% per year to about 10% per year. And so the burden of rust is higher, so that means the propensity that it's going to involve the car, and if that is a lot higher than if it's just a little bit and the location is closer to the important parts of the car.

And, smoldering multiple myeloma is an area of active interest that, when we think about the goal in medicine is we want to prevent something bad from happening. So, that's why we talk about screening for colon cancer. We recommend colonoscopies, because if you catch a polyp early, you could prevent somebody from developing colon cancer. We talk about mammograms, so if we detect an abnormality, we can prevent the evolution to breast cancer.

And smoldering is an area where we're trying to apply that same analogy; but it's a little bit different in the sense that we're going from solid cancers to a blood cancer. And that's an area of active interest. The data for it is rapidly evolving. And speaking of active research, there was a study that recently showed that if you use this drug, for example, daratumumab as a single agent in smoldering multiple myeloma, you could prevent progression to active disease. And it's been FDA approved for that.

And I think the challenge right now, I if you ask the multiple myeloma community, there is a lot of heterogeneity in terms of how we apply that to practice. I think the challenge is we haven't identified the patient that's saying- Oh, ideally it would be nice to know this patient is going to 100% develop myeloma; and we need to treat that patient versus there are patients who have smoldering where nothing's ever going to happen. We're getting better and better, but we haven't quite reached that.

But nevertheless, I think it is important that we do have this daratumumab as option. So, this is a conversation with the patient, the caregiver, and the oncologist about, should you use the daratumumab for patients with smoldering multiple myeloma?

Elissa: Yeah, that is great to hear that you can prevent some progression to myeloma with that. That's really exciting.

Dr. Yee: Right.

Elissa: So, I wanted to ask about other patients with myeloma also may have AL amyloidosis as a secondary diagnosis. What is that, and why is it something that can happen along with myeloma?

Dr. Yee: Yeah. So AL amyloidosis is a condition that we see. Well, let's step back a second. What is amyloidosis in the first place?

So, amyloidosis refers to a condition where abnormal amyloid protein is being deposited in a place where it shouldn't be. And it turns out that there are different kinds of amyloidosis because I know patients will start to hear about amyloidosis, and then it turns out there are different kinds. But, that's what we're talking about.

<u>Elissa</u>: Yeah, yeah.

<u>Dr. Yee</u>: So, there's amyloid protein that forms, involved in dementia; but this is, when I think about AL amyloidosis, it's not related. There's no relationship.

<u>Elissa</u>: Okay.

<u>Dr. Yee</u>: There are different kinds of amyloid; and the two most common kinds of amyloid that clinicians will and can encounter are AL amyloidosis versus TTR amyloidosis. So, in AL amyloidosis, the AL stands for, the L stands for light chain. So, the source of the amyloid protein in AL amyloidosis is abnormal light chain that's being misfolded to make amyloid deposits. And then the source of that light chain is from abnormal plasma cells from the bone marrow. So, AL amyloidosis is a plasma cell condition that overlaps with multiple myeloma.

Then, there is TTR amyloid, which people will hear a lot about because TTR amyloid can involve the heart. But it turns out that in TTR amyloid, the TTR stands for transthyretin, and the source of that is from the liver. So they both have the word "amyloid," but the source is different.

Now, another way of thinking about this would be amyloid just refers to what it looks like under the microscope but doesn't tell you what the source is. So, it would be, like if you go to a restaurant and they serve you a piece of white food, it could be anything, right? A piece of white food could be pork, it could be chicken, it could be fish, it could be cheese, it could be tofu, right? It all looks white on your plate. But it's very different because you wouldn't serve a piece of chicken to somebody who's vegetarian.

Elissa: Right.

Dr. Yee: That's why it's important to make the distinction between AL and TTR amyloid because the treatment is completely different.

So let's just focus on AL amyloidosis. In AL amyloidosis, it refers to abnormal protein deposits being formed by abnormal light chain which is being formed by abnormal plasma cells. And generally speaking, these plasma cells are abnormal. If you look under the microscope, they could look very similar to the cells that cause multiple myeloma because, again, myeloma's a cancer of plasma cells; and AL amyloidosis is a condition from abnormal plasma cells. So, there's a lot of overlap between the two.

And in terms of the clinical manifestations, I just talked about protein deposits, so, where could these proteins deposit? They can deposit in the heart. It can affect the heart function so shortness of breath can be a major manifestation of it. It can deposit in the kidney, and it can affect the kidney's ability to function where it can leak. It affects the filter of the kidney.

The kidney's job is to put the waste and the urine and to keep your cells in the blood and regular proteins in the blood. But if AL amyloid affects the kidney, it can cause it to leak regular protein in the urine. And, amyloid can also deposit in the liver, can deposit in the nerves. But the most common organs are the heart and the kidney, and some patients can have both heart and kidney involved. So, because of the relationship, the treatment for AL amyloidosis has a lot of overlap with multiple myeloma. So, the drugs we use for multiple myeloma, in many cases, we can use the same exact drugs in AL amyloidosis because the goal of treatment is to shut down the source of the protein, which is the plasma cell that's misbehaving.

Elissa: Okay.

Dr. Yee: So that's why a patient could definitely have myeloma; and then they could have secondary AL amyloid. And then you can have patients that may present with AL amyloidosis as their main manifestation, and then they can develop myeloma down the road. So, there's some crossover.

The challenge is, and I think this is where it gets complicated for clinicians, if somebody has a bone marrow biopsy, it can show abnormal plasma cells. And the pathologist will just say bone marrow biopsy shows abnormal plasma cells; but the pathologist doesn't know the patient.

The same bone marrow biopsy can be seen in a patient who has multiple myeloma. The same bone marrow biopsy can be seen in somebody who has AL amyloidosis, and the same bone marrow biopsy can be seen in somebody with smoldering multiple myeloma. So, that's where the medical oncologist comes into play.

Elissa: So, you started talking a little bit about treatments. What are the current treatments for multiple myeloma?

Dr. Yee: So, for people who take care of multiple myeloma patients, it's been a really exciting period becauseover the course of the time I've taken care of patients, we've seen so many drug approvals, as well as not only do we have drugs approved, but we also have all these new combinations of using these drugs together. And that's why for us and Blood Cancer United's has played a key role in helping to get these drugs approved and the research behind it. So, I think the myeloma community is really thankful for that as well.

And the treatments have evolved significantly over the years. So, there are three core drug classes in multiple myeloma. The first two classes came about 20 years ago. And we think about immunomodulatory drugs like thalidomide, lenalidomide, and pomalidomide. So, for newly diagnosed patients, lenalidomide is the immunomodulatory drug that's used. And it turns out that lenalidomide is very closely related to thalidomide. And you may recall that thalidomide, has a terrible history, right? In the late 1950s in Europe, babies were being born with missing arms and legs because their mothers who were pregnant happened to take thalidomide for morning sickness.

Elissa: Oh.

Dr. Yee: And it turns out that thalidomide went from being this drug nobody wanted anything to do with from that awful history; but it turns out that, there was a dermatologist in Israel who had patients with a rash related to leprosy. And this rash was keeping these patients up at night, so this dermatologist gave these patients thalidomide, knowing that the thalidomide would help them fall asleep, right? And it turned out the rash got better on that medication, so then that led to the observation that, "Wait, if this drug can help this rash from leprosy, maybe it has other medicinal properties." And then eventually it led to the discovery that this drug thalidomide works amazing in multiple myeloma.

And then there's a closely related drug, lenalidomide, that doesn't have the side effect. Thalidomide's associated with sleepiness and constipation and neuropathy; and lenalidomide doesn't have that as the side effect. So, that's why we use lenalidomide. And it turns out the lenalidomide causes degradation of these transcription factors, Ikaros and Aiolos. So, these are proteins that are important to the survival of myeloma cells; and this drug, lenalidomide, causes those growth signals to be depleted in the myeloma cell. So, that's drug been a game-changer in myeloma.

So, the second class of drugs we have are the proteasome inhibitors. So, we think about drugs like bortezomib, carfilzomib, ixazomib, also known as VELCADE®,KYPROLIS®, NINLARO®. And so, this is a second core class of drugs that we use in myeloma; and these drugs inhibit the proteasome, which is kind of the garbage can of cells. When I think about on a construction site, you need to have a dumpster, right, because if you're building a house, there's always a dumpster outside the house because they're building stuff. They got to find a way to get rid of the waste. And myeloma cells make a lot of protein, right? They're making that monoclonal protein; and so they really are dependent on that garbage can. So, the proteasome inhibitor inhibits that garbage can.

And then the third class of drugs is the anti-CD38 monoclonal antibodies. And CD38 is a protein that's on the surface of plasma cells and myeloma cells, right? And so, we have two approved anti-CD38 monoclonal antibodies. You have daratumumab, also known as DARZALEX®. Then we have isatuximab, also known as SARCLISA®. So, these are the three core drug classes: the immunomodulatory drugs, the proteasome inhibitors, and the anti-CD38 monoclonal antibodies. And the evolution over the past two decades has been to combine these drugs. So, we went from two drugs to three-drug combinations. So, we have the three-drug. We call it RVd, Revlimid-Velcade-dex.

And then because this has been based on clinical trials. So, people have done clinical trials; and it shows that, the three drugs like RVd is better than Rd. And then the recent innovation in the past few years has been looking at four-drug combinations. I know, it's a little bit complicated because I just went from saying three to four drugs. That fourth drug, though we only talk about is dexamethasone and corticosteroids.

So, corticosteroids is another key component of myeloma therapy. Now, it's not technically chemotherapy, right? So, dexamethasone by itself can kill myeloma cells. And so, the combination of all four drugs together, CD30 antibody, a proteasome inhibitor, an immunomodulatory, and dexamethasone works better. The total is more than the sum of its parts.

And so, one of the innovations in the past few years has really been looking at a four-drug combination. So, for newly diagnosed patients, older patients, younger patients, a four-drug combination has been an emerging standard for patients. And that's based on randomized studies. So, the majority of patients, we tend to use a four-drug combination.

Elissa: Okay.

Dr. Yee: And then we talk about the side effects, right, because then, next question, I think when I see new patients, questions that come up would be, "What are the side effects, and what's the schedule?" Right?

Elissa: Yeah.

Dr. Yee: When I think about the side effects, we can break it down to several. So, we think about the immunomodulatory drugs like lenalidomide. The side effects that are important to emphasize, well, (a), you can't get pregnant on this drug because it's closely related to thalidomide. Or you can't get somebody pregnant. And there's all this paperwork related to it because of its heritage in relationship to thalidomide.

It can be associated with low blood counts; and there's always a risk of blood clot. So, that's why we typically recommend aspirin to minimize the risk of blood clot. Longer term, there can be risk of a second cancer, and the longer-term patients can have, diarrhea with this treatment. And then when we think about the proteasome inhibitors like bortezomib, a key thing we think about is it can cause peripheral neuropathy, so, that can be numbness and tingling of the feet.

And another less common side effect, but it's something that people don't talk about, it can cause styes involving the eyelids. So, it can cause a thing called blepharitis. So, neuropathy is tingling of the feet, as well as blepharitis.

The CD30 antibodies, since they're more targeted against CD38, their side effect profile is much easier than the other two classes. So, I don't really hear a whole lot of complaints about this CD30, like daratumumab or isatuximab. But in combinations, you can have accentuation of low blood counts and infection.

And then there's the dexamethasone. So, of the four drugs I've just talked about, the dexamethasone is where I hear the most complaints. Some patients love the dexamethasone. What people love about the dex is that they can have like a surge of energy when they have dexamethasone. They have great energy; and it's a corticosteroid, so it's a powerful anti-inflammatory. So, pain can go away. If you have aches, muscle aches, pain from whatever, dexamethasone can have the potential to seriously improve that. So, patients love the burst of energy, as well as the anti-inflammatory properties.

But then the other side of the equation, the patients don't like trouble sleeping. It can make mood changes. Like trouble sleeping's a big one. Mood changes, irritability, it can increase your appetite, weight gain, affect your blood sugars. Longer term, increase your risk of cataracts.

And then because of the surge in energy, there can be this seesaw effect where people can have a burst of energy. When I have a new patient, usually they're really anxious about the first day of therapy. But actually, patients feel great on the first day of therapy because they're getting the dexamethasone. Nobody's complaining about that first day.

But, if you get the treatment on a Monday, you know, Tuesday you feel fine. But then, Thursday and Friday, there can a lull in the energy because they have this high from the dex and then they have this crash. And so, of the four drugs, the dexamethasone is the one I adjust the most, the dosing of. And I think increasingly, dexamethasone, it's like bacon. It's great if you put it on a burger, potatoes. Everybody likes bacon, right? But you can have too much bacon. So, I think one thing we're appreciating in the past year or two is that we have to dial back the dexamethasone amounts to improve the tolerability. So, before, historically, we used to use a lot more; but now we're starting to dial it back.

So, in terms of the overall patient experience, I think that a lot of it is driven by the dexamethasone. And then second to that, I have to think about the neuropathy from bortezomib is something I always ask patients about because that can kind of creep up on patients, not right away; but, after a month or two months of treatment, it can start to show up in the feet. And if patients start to develop that, that's something we think about dialing down the dose and pausing the therapy. If patients have ongoing fatigue, sometimes we think about the lenalidomide and then we can dial down the dose of that.

But I think the common theme here is that when we see a patient with myeloma, we're on this journey together; and there are lots of visits. And our goal here is to make the experience as user friendly as possible for the patient because it's a long treatment; and it's kind of complicated, and we're in it together. And we have to make adjustments to make it as smooth as possible.

So, going back to the schedule the treatment can be pretty involved in the beginning. So, it can be weekly visits. In some patients, it can be twice a week. But the first couple months, it's weekly. And then months three through six, it could be like three out of four weeks. So, the first six months, it's pretty busy. So, then, onward, it can be like once a month, for example.

And then the exact schedule could differ. Every patient practice has their preferences. It's sort of like you go to different restaurants, they might like doing things their own way. So, it's not like the one way is the right way.

So, that's what I mean. In the beginning, myeloma is front and center because the schedule's pretty involved. But then once you get through the first year, the schedule is a lot better. I think the first-year people, it's so busy that they don't have a chance to think about vacation, right? But then you start to think about doing normal things like planning vacation, doing things.

Elissa: That's great. And I'm glad you brought up side effects, and it sounds like they can be managed, which is great news. So, that sounds like it makes it really important then for patients to communicate with their doctors then, right, when they are having these side effects so that you can try to mitigate those?

Dr. Yee: Yeah, because we want to hear about them.

Elissa: Yeah.

Dr. Yee: It's not like you're taking an antibiotic for seven days or something. This is a long treatment, and we want to make sure that we try to optimize things for patients.

Elissa: Yeah. So, I want to ask about a few other treatments. So, one is autologous transplant that patients may have. Could you talk a little bit about that and what that is and when patients might have that?

Dr. Yee: Right. Autologous stem cell transplant can be another core component of someone's therapy. And a couple of things. So, when you hear transplant, the first thing you think about, oh, there's going to be a surgeon and there's going to be a knife involved, right?

Elissa: Yeah.

Dr. Yee: That's what transplant sounds like. But there's no knife, and there's no surgeon involved.

Elissa: Good.

Dr. Yee: So, autologous stem cell transplant refers to transplanting your own stem cells. But just thinking more broadly, what's doing the heavy lifting in the transplant is the high-dose melphalan. So, when we think about autologous stem cell transplant, think more about getting high-dose chemotherapy.

So, a lot of these drugs that we've been talking about, the three drugs, like the immunomodulatory drugs, the proteasome inhibitors, the CD30 antibodies, it's really only been in the past 20 years. But before we had those drug classes, for patients to get a response, you needed to give patients high-dose chemotherapy because we didn't have drugs like lenalidomide. We didn't have bortezomib. We didn't have CD30 antibodies. So back then, you needed high-dose chemotherapy to get a response.

So, one of the innovations was this idea of collecting stem cells ahead of time. So, these are your own stem cells. And when I think about stem cells, I think about like the queen bee. So, if you take a queen bee and you put her into an empty beehive, she can recreate the whole beehive, right?

So, the stem cells, like the queen bee, where these cells can recreate your whole bone marrow from scratch. And there are ways to collect these stem cells, to go into your circulation as if you're donating blood. And then they're collected and then they're put in the freezer. And then it's kind of like from *Empire Strikes Back*, like Han Solo. He was kind of put in that deep freeze. So, they're kept in the freezer.

And then patients get this big, heavy-duty chemotherapy; and that's to clean out the beehive, so to speak of myeloma cells. And then the stem cells get thawed, and then they're put back into you. Right, and so those stem cells get put back into you; and the stem cells are there to help you recover faster from the high-dose chemotherapy. So, instead of having low blood counts for weeks and weeks, it's a much shorter period of time. So, the transplant is a form of supportive therapy. But the heavy lifting is being done by the high-dose chemotherapy.

Now, getting the high-dose chemotherapy doesn't cure patients of myeloma. It's another way of getting a deeper response. Now, something to think about is you may have noticed when I talked about the four-drug combination, a couple things I did not mention for side effects, I didn't mention hair loss and I didn't really mention a whole lot of nausea or GI (gastrointestinal) side effects, right? I talked about change in energy, and I did talk about neuropathy. But when you get high-dose chemotherapy, I think about as high-dose, old-fashioned chemotherapy. So, old-fashioned chemotherapy wasn't very selective. High-dose chemotherapy targets the core machinery of cells in general; and when you target the core machinery of cells in general, you have old-fashioned side effects from old-fashioned chemotherapy. So, old-fashioned side effects can include hair loss. That's like guaranteed. And nausea, diarrhea. And because it's heavy-duty chemotherapy, it's not for everybody. So, we tend to think about this for younger, fitter patients.

Elissa: Right.

Dr. Yee: This is a really complicated topic talking about which patients should get high-dose chemotherapy because I think this is an area where you'll see some heterogeneity in practice across the country where it's incorporated more as part of the treatment paradigm because we do know that if you get high-dose chemotherapy, you will definitely get a deeper response. Everyone is in agreement that if you get high-dose chemotherapy, you will get a deeper response.

And we do know as a general statement, deeper responses tend to translate into better outcomes. But already with four-drug regimens, you already do get a really deep response. So, the question, the challenge that comes up is like which patients should get, and do you have to go through all that to get an even deeper response? So, that's an emerging area where I don't think the dust is fully settled. So, yes, there are patients where I do recommend getting high-dose chemotherapy just based on certain clinical characteristics. But then I have other patients where I don't feel as strongly about the high-dose chemotherapy. And it is a very individualized decision between the patient, the caregiver, and the treating team.

Elissa: Now, do myeloma patients ever get allogeneic transplant, so stem cells from a donor?

Dr. Yee: So, in an autologous stem cell transplant, these stem cells are coming from yourself. In allogeneic stem cell transplant, these stem cells are coming from somebody else. They're coming from a donor. So, when people talk about those donor drives to get the marrow, that's from looking for stem cells from somebody else.

Elissa: Right.

Dr. Yee: And the allogeneic transplant, I think, is more commonly used in acute myelogenous leukemia for that kind of blood cancer. And in multiple myeloma, it was used more. But since the advent of these therapies that we were just talking about, it's not used that commonly. So, it's pretty uncommon to have a patient being referred for an allogeneic stem cell transplant because in addition to these therapies we were just talking about, we have all these other therapies which have been available to us in the past five years. And these are therapies such as CAR T-cell therapies, such as bispecific antibodies. And these therapies, remember I was so excited about how transformational about the immunomodulatory drugs, the proteasome inhibitors, the CD30 antibodies? Those therapies were transformational when they arrived. And we have these newer therapies which are approved in the past, just in the past five years; and I think they have the potential to be just as transformational.

<u>Elissa</u>: That is exciting.

So, a couple treatments I wanted you to just cover really briefly are CAR T-cell therapy and bispecifics. Are those things that are currently approved for myeloma treatment?

<u>Dr. Yee</u>: Right. So, the CAR T-cell therapies and bispecific antibodies, we're really excited about them now since they have the capacity to be just as transformational as the therapies that I was just discussing earlier.

<u>Elissa</u>: Yeah.

<u>Dr. Yee</u>: So, CAR T-cell therapies and bispecific antibodies, these therapies were just approved in the past five years. So, let's just spend a little bit time talking about these therapies. So, CAR T-cell therapies are a living drug. They're taking your own white blood cells, and they're modifying them to attack myeloma cells. So, think about right now your white blood cells can attack bacteria, they can attack viruses, right? But what if you could take those same white blood cells and train them and reprogram them genetically so that instead of attacking bacteria or viruses, they attack myeloma cells instead? That's what a CAR T-cell is; it's a chimeric antigen receptor T cell where the receptor's been reprogrammed. And what is it targeting? It's a new target called BCMA, B-cell maturation antigen.

So, we talked about how CD38 is on plasma cells. It's a cell surface protein. Well, another cell surface protein is BCMA, so you can take your own white blood cells. They can be genetically modified, so they can attack BCMA, which is on the surface of plasma cells and myeloma cells. So, that's one way of targeting BCMA.

A different way of targeting BCMA are bispecific antibodies. So, what does the bi mean? Bi means it's two things. It's targeting two proteins. So, in a bispecific antibody, it can bind to BCMA; and it can also bind to CD3 on the surface of T cells. So, a bispecific antibody brings the T cell directly to the myeloma cell.

And so, these are therapies we have now. Before they were in clinical trials, and now we are fortunate enough to be able to offer them to our patients as regular standard of care. And currently, at the time of this recording, the bispecific antibodies are approved in patients with four prior lines of therapy. And then we have two CAR T-cell therapies that are approved in patients with one or two prior lines of therapy.

Elissa: Oh.

Dr. Yee: And for many of our patients, these therapies can offer incredible responses for patients. For patients on these therapies, they've been telling me that this is like the best they've ever felt.

So why is that, right? So, in a CAR T-cell therapy, what is amazing about this living drug, it offers the ability for a one-and-done type treatment. Right, so patients, when they get to the point where they think about CAR T-cell therapy, they've sort of had it with coming in over and over for treatment, right? So, with a CAR T-cell therapy, you have the chance to get a therapy; and then you're in observation afterwards. And patients love that. So, they can be going from lots of visits for treatment to being off therapy and being observed.

Now, the CAR T-cell therapy, because it's a living drug, it's a little bit of work to make a living drug, right? It's not off the shelf. You can't just walk into your pharmacy and pick this up. And you can't just walk into your infusion unit and get this injection or infusion. So, for CAR T-cell therapy, you have to get your white blood cells collected, similar to donating blood and similar to the stem cell collection. But here we're not interested in the stem cells. We're interested in the lymphocytes.

And these lymphocytes are collected as if you're donating blood, and then they are sent to a company where they're reprogrammed. And it takes about a month or six weeks for them to be reprogrammed. Once they're manufactured, patients do have to get about three days' worth of chemotherapy to make space for these lymphocytes to expand.

Elissa: Okay.

Dr. Yee: And so, when you get the infusion and then they expand, that's when they start going after your myeloma cells in the patient.

So, the next question, what are the side effects of this treatment? This is a living drug. These are living white blood cells. And think about when you fight an infection, like if you have a cold, fevers are pretty common, right? So, guess what? When these white blood cells are fighting myeloma cells in your body, fever is pretty common because they're battling your myeloma cells. So, instead of battling an infection, they're battling the myeloma cells. So, fever is very common. That means that these cells are doing their business. And they're releasing of cytokines. So, fever is a common manifestation of cytokine release syndrome (CRS).

Now, if it's a really protracted battle, sometimes in cytokine release syndrome, you can have low blood pressure and need for oxygen. And so that's why these therapies are kind of given in a major medical center because you have to be ready to deal with low blood pressure or need for oxygen. But, fortunately, we have these supportive therapies; and we have ways of calming down the immune system to help reverse when the immune system goes a little bit too much. We have drugs to do that.

And then, patients are monitored for other short-term side effects like a kind of chemo fog or, we call it, neurotoxicity. But again, I think the important thing is these are things that are short term. And when patients go home, those side effects are behind you. Now, there are some rarer side effects, longer-term side effects from CAR T that you can have delayed neurotoxicity; but that's less common. But, again, it does emphasize that it's important that this is being done in a major medical center. But the same time, it does limit to how widely applicable this is.

Elissa: Yeah.

Dr. Yee: But the bispecific antibodies, they also target the same thing. And the nice thing about the bispecific antibodies is that they are more immediately accessible. It's not a living drug. It's something that an infusion unit they just give you right then and there.

And also targets BCMA; and you can see great responses, but you do have to be monitored for cytokine release syndrome and neurotoxicity. So right now, it's not as easy to give as like the bortezomib or the daratumumab, right? Those are relatively easy to give, whereas these bispecifics, there's a little bit more work involved for the monitoring for these side effects. And sometimes it happens at the hospital, but sometimes they're starting to explore doing it as an outpatient.

And I think the exciting thing with these therapies is, remember all the excitement I said about these four-drug combinations for newly diagnosed patients? It turns out that these therapies, we're starting to evaluate them at earlier stages of the myeloma journey. So, right now the bispecific antibodies are approved in four prior lines of therapy; but we heard data at this recent ASH® (American Society of Hematology Annual Meeting and Exposition) about looking at one to three prior lines. And we also started hearing more and more data about these bispecific antibodies in newly diagnosed patients. The responses we were seeing are incredible, probably better than the four-drug regimen.

Lizette: Wow.

Elissa: Wow.

Dr. Yee: So, but, and we do need clinical trials; and that's why participation in clinical trials is really vital. They're voluntary participants and we appreciate the time that they put into it because it's really through the patients in the prior trials that we gain access to these newer therapies and we understand how well these drugs work, as well as also learn about potential side effects as well.

But, I think in the years ahead, we're going to see even better responses, patients doing even better, living longer. And I said in the very beginning when we first started talking that, we don't think of myeloma as being curable. But I think we're starting to see some hints some of the patients could be potentially cured with these therapies. We just don't know that yet because we haven't had long enough follow-up, which is really what's so incredible about the times we're living in.

Elissa: Wow. Well, it sounds like the future is really exciting. I'm so glad to hear about things potentially moving, closer to the frontline and all these wonderful combination treatments as well. And oral treatments that patients can take at home without having to be in the hospital is just so exciting.

So, our final question for you today, 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. Yee: I completely agree that after diagnosis comes hope because when I see patients, they're having the worst time of their life. And I think what I'm so hopeful for is that we have these therapies that can get people back in the saddle. And that this is just the beginning and that better days are certainly ahead; and that we're in this together. It's a team. Patients can go from having, again, I talked about how something's on the front burner. So, this is just something in the background. And I think it's really through Blood Cancer United, the work that they do, as well as the patient support, caregivers, it's like through this team process, we can really have amazing outcomes for patients.

And that's why whenever I talk about this, I'm so excited because these therapies really are that exciting. I see these patients all the time in our clinic, how they were in a tough spot; and now they're just living their best life. And they're moving forward with their lives.

Elissa: That is wonderful. And I think everybody listening today can hear how excited you are about all of these treatments. And I think that gives people hope, just with that. That if you're excited, they should be excited with all the different treatments available and possibilities for the future. And so, thank you so much, Dr. Yee, for coming on the podcast today and explaining this in a really neat way. I love the cannoli analogy. So, we really, really appreciate you joining us today; and thank you so much.

Dr. Yee: Well, thank you so much for having me; and thank you for giving me the chance to share my enthusiasm for all these therapies and the journey. Thank you.

Lizette: Thank you.

Elissa: 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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