[MUSIC PLAYING]

ANGELA DISPENZIERI: Hello, my name is Angela Dispenzieri, and I am a doctor at the Mayo Clinic. I'm a hematologist, a professor of medicine and laboratory medicine, and today I'd like to talk to you about AL amyloidosis treatment, including high-dose chemotherapy with stem cell transplantation.

So just a very brief introduction about what AL amyloidosis is. It's one of many different types of amyloidosis, and here you can see a list of a number of different types of amyloidoses. Amyloid is a disease where different proteins, for whatever reason, and we don't always understand it very well, decide to basically group together in what we call amyloid fibrils. AL, the building block protein, or precursor protein, is made of immunoglobulin, most commonly immunoglobulin light chain. And this is a disease that can affect the heart, the kidney, the liver, the nerves, the skin, soft tissues.

You can see that there are a number of other types of amyloids, which are very different diseases, but they share in common that they have these fibrils, which under the microscope are perceived as what we call amyloid. The bulk of the diseases that I have listed there are actually hereditary forms. The good news is that AL is not a hereditary form of amyloid. It's something that's acquired, and if a person has it, it's not something that they should worry about that their family members are going to be affected.

So we're going to move on now to what this is. And so here's a cartoon of a person, and you can see a blow-up that there's bone marrow. So that's a shot of part of the pelvis, where a lot of bone marrow is. And so AL is actually a bone marrow disease. In the bone marrow, there are a number of different types of cells. Plasma cells are cells that we all have. They're actually immune cells. They help us fight off infection, and that's what happens in health.

And the job of these plasma cells is they make these proteins that are represented by kind of those Y's that you can see on the slides. Those are called antibodies, or immunoglobulins. And again, in health, these are really important, and they protect us. These immunoglobulins can be intact so that they're kind of made of four pieces: two smaller pieces, which are called light chains; and two heavier pieces, which are called heavy chains.

You can also see on the slide that those smaller pieces can sort of move off on their own, and we call those free light chains. So in some people, for reasons that we don't fully understand, there can be this overgrowth of these plasma cells in the bone marrow. And because these are the manufacturing sites of these immunoglobulins-- and most importantly, these free light chains-- if you have more manufacturing plants, you end up with more of that product, these free light chains that can be circulating in the bloodstream.

And in patients who have this tendency towards amyloidosis, these free light chains can sort of line up into these little fibrils, or almost think of fibers, that then can deposit in the various tissues. AL likes to infiltrate or deposit in the heart and the kidneys, most commonly. It also can sometimes deposit in the liver or the nerves. It can deposit in the skin and the soft tissue ligaments. And again, putting this protein, this gunky stuff, in places it doesn't belong can actually make people feel unwell and, of course, threaten their quality of life and their life span.

So what do we do about this? How does one treat AL amyloidosis? So the strategies are sort of really two major categories. One is kill those plasma cells. So I showed you those plasma cells that reside in the bone marrow. If we can wipe those out, then we can't make any more of those immunoglobulins, and hopefully life would be good. Another approach would be to pull amyloid from the tissues. I said to you that the amyloid is sort of mucking up the works, and so if we had an amyloid vacuum cleaner, some way of actually pulling it out of the tissues, that would be wonderful.

In current day, there isn't any types of drugs that really work to do that that we know of, but the good news is that there's several drugs, experimental drugs in clinical trials, whose goal or mechanism of action is to really draw that amyloid from the tissues. So more to follow on that. But again, our major path outside of clinical trials, experimental clinical trials, is to kill those plasma cells. So how do we do that?

Well, we use a combination of drugs, chemotherapies actually. And one of the most common combinations is the combination of something called bortezomib, dexamethasone, and cyclophosphamide. Sometimes cyclophosphamide is replaced by a drug called melphalan. There are other medications, like Pomalidomide and lenalidomide, that are used and often combined with dexamethasone. There are other drugs that are used for multiple myeloma.

Now amyloid is a cousin disease to multiple myeloma. Both are diseases where there's an overgrowth of these plasma cells in the bone marrow. So myeloma is about five times more common than AL amyloidosis, and so we can borrow from their armamentarium. And as drugs are developed for multiple myeloma, we can try to see if we can use them in patients with AL amyloid.

We know that often these drugs have more side effects in patients with AL than they do with multiple myeloma, so we don't always just take a myeloma drug and just throw it in the direction of an AL patient. And we mix and match, and so there's a lot of different combinations, which I'm not listing right here. But we can swap drugs around to try to make that work for us. There are a number of really interesting drugs that are in clinical trials for myeloma that we're starting to try in patients with AL amyloid. One of them is called Venetoclax. Another is called daratumumab, et cetera. So that list will hopefully grow and grow so we can be very effective at treating patients with AL.

Another therapy that we use is high-dose melphalan with stem cell transplant, or stem cell transplant, or some call it bone marrow transplant or autologous stem cell transplant, which is another way of killing plasma cells. So each and every one of those dots that I have listed under killing plasma cells, they all have the exact same goal: get rid of those plasma cells so they can't make any more of those bad immunoglobulins, those bad light chains. And then allow the body to number one, not get worse, and number two, to actually heal faster.

So the body knows that amyloid doesn't belong in the tissues. It's just not very effective at drawing it out itself. It does it, but it does it very slowly. And the metaphor I like to use is that if you imagine that you have 1,000 guys laying bricks to build a wall, and there's one poor soul at the back trying to take that wall down, he's not going to do very well. The 1,000 guys are just going to keep laying brick after brick after brick, and that wall is going to get bigger and bigger. So that amyloid is going to get worse and worse.

However, if you can get rid of those 1,000 guys, make them go away, then that guy at the back of the line, which is actually your body, or a patient's body, trying to heal, then that sole individual, so to speak, can actually pick away and get rid of the amyloid. And then that will reduce the amyloid burden in the body and make a patient better.

And so the question is what is high-dose chemotherapy with stem cell transplant? It's basically just like the chemotherapy I mentioned, the other chemotherapies I mentioned. It's trying to get rid of those plasma cells, and so it's kind of a mother of all chemotherapies in that it basically is very high doses of a drug called melphalan that are given to a patient. Now, if we give those very high doses of chemotherapy, we know that we can kill probably more plasma cells than a lot of the other drugs that I already listed to you.

That may change over time, however. Some of our drugs may be as effective as using really high doses of melphalan. That's a work in progress. But if a physician were to give very high doses of chemotherapy, high doses of melphalan, to a patient, they would kill a lot of plasma cells in the vast majority of patients.

However, there would be collateral damage. Those other bone marrow cells that are normal cells that we all rely on to help us fight infection or to give us clotting cells called platelets or to help us carry oxygen with our red blood cells, those would be irreparably damaged. And we wouldn't be able to make those things anymore. So that would be a bad thing.

So somebody came up with the idea, can we have the best of both worlds? Can we perhaps basically give the high-dose chemotherapy, but give seed cells back to the patient so that they can regrow the good stuff? They can regrow those normal red cells and platelets and other important white cells. And so that was the birth of stem cell transplant. And so the mechanism by which we do this high-dose chemotherapy is first we need to get the seed cells from the patient ahead of time. And so we can collect those seeds through a tricky process called stem cell collection.

We can basically give some shots that coax bone marrow seed cells into the blood cells, so good seed cells into the bloodstream, and then we can do a procedure called leukapheresis that basically we can just with a session, where a patient just lays in a chair or a bed for about five hours, we can sort of skim off the seed cells and then collect those and put them in the freezer so they are ready to go for the patient when they need them.

And then what we do is we give those very high doses of chemotherapy through the vein, and then when the chemotherapy has left the body, which is usually about 24 hours or less, we can actually give those seed cells back. And what happens is those seeds cells are given through the bloodstream. They home in to the bone marrow and start growing. So we're trying here, again, to get the best of both worlds. We're giving really high doses of chemotherapy to get rid of as many plasma cells as possible, and then we're regenerating our bone marrow so that we don't have a transfusion need ongoing.

During the course of two to three weeks, while a patient is sick from the chemotherapy and before the seed cells have grown back in, people will need transfusions and antibiotics and other types of supportive care. But once they've gotten through that, then basically we look to see have we achieved our goals and reduced the number of plasma cells, reduced the number of light chains? And then hopefully set the patient on their road to recovery.

And so, again, whether it's a stem cell transplant, or whether it's other types of chemotherapy, the approach is the same. The approach is to get rid of the plasma cells, get rid of the light chains that can make the amyloid. Now the other piece that I didn't mention yet is that the amyloid fibrils that get into the organs can be toxic, but those free light chains that have the ability to turn into amyloid also can be toxic in their own right. And so each of these approaches that I've talked to you, again, are doing the same thing: getting rid of the plasma cells, getting rid of the light chains, and hopefully getting rid of the amyloid so that there, over a period of time, can be healing.

So people often ask which therapy is best? And there's a question as to whether the transplant itself is the best therapy, and that's a really hard question to answer because really often the healthiest patients are the ones that are offered the transplant, because giving those very high doses of chemotherapy not only affect the bone marrow-- the normal bone marrow elements that I told you could be a bad thing, and that's why we have to give those seeds back-- but it can also be toxic or poisonous to other organs.

It can make people very sick to their stomach, and it puts a real strain on the system. And if a patient with AL amyloidosis is already rather sick from the disease, that their heart doesn't work very well or their liver or kidneys don't work very well, then they can get into trouble, and the transplant can be life-threatening. And patients can even die related to the procedure. And so we have to be very cautious in how we select the patients that move to the transplant.

In turn, results of transplant typically will look a little better overall than the treatments that we use in patients who we don't offer transplant to, because the sicker patients are not typically offered the stem cell transplant, and the healthier patients are. And intuitively, healthy patients tend to do better than sicker patients, and so that can skew those results.

As our treatments improve to kill plasma cells with all these new medications that I've already mentioned, drugs like bortezomib and some of these other drugs that are up and coming that we're using for myeloma, it may well be that transplant won't even be necessary, that these other drugs will achieve the same end, that they will kill plasma cells well and durably.

Unfortunately, these therapies don't work for everybody. Even transplant doesn't work for everybody. But we have a lot of other options. As I showed you, we can try Plan A, Plan B, et cetera, and hopefully we can improve patients, not only their quality of life, but also their longevity. And we certainly have done that over the course of the past decades with patients living two, three, four, five times as long as they had historically.

And so we're very excited about the progress that we're making, but we still have a long way to go. And through collaboration and centers of excellence like the Mayo Clinic, advances can be made. And hopefully there will be more and more patients that derive benefit and derive benefit more easily without so many side effects, and that they can live long, healthy lives.

There are a few must do's if somebody is diagnosed with amyloid, and I just want to run through these briefly. The important part is that a patient must establish the type, or the building blocks, of the amyloidosis. On one of the first slides I showed you, I pointed out that there are different building blocks. And the chemotherapies I just told you about only are used for the AL type. You have to understand which of your organs are most at risk. You have to consult with an amyloidosis specialist to design a plan for you.

This is important because it's a very rare disease. Eight in a million per year, and so one needs to understand this disease in order to offer the best supportive care and the best therapeutic plan. And then learn which parameters are most important to follow your disease. The light chains are typically among the most important things to follow, but there are other blood markers, be it chemicals in the blood like NT-proBNP or troponin, alkaline phosphatase, serum albumin, creatinine, urine total protein, et cetera, to follow.

And one must maintain hope. As I mentioned, there's been a lot of progress in this disease. It's important to take good care of yourself in other ways, good diet and exercise regime. And finally, maintain a good support network. And with that, I would like to thank you for your time and attention.