FAQs on Multiple Myeloma Diagnosis and Prognosis

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Transcript

Mary DeRome (MMRF): Thank you for joining us for today's session, Frequently Asked Questions on Multiple Myeloma. I'm Mary DeRome, Senior Director of Medical Communications and Education at the Multiple Myeloma Research Foundation. I'm joined today by Dr. Benjamin Derman and Ms. Sarah Major from the University of Chicago and their patient Julia Grosch from Aurora, Illinois.

We've invited them here today to answer some of the frequently asked questions we receive from patients and caregivers when they've received a diagnosis of multiple myeloma.

Our first set of questions is going to focus on the multiple myeloma precursor conditions, monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma.

Dr. Derman, can you tell us how it is determined if a patient has a precursor condition, versus myeloma? And do these conditions always proceed to myeloma, and if so, by how many months or years?

Benjamin A. Derman, MD: Thanks for inviting us. We're so happy to be here. When we talk about precursor conditions like MGUS, and smoldering myeloma, these refer to states where a lot of the features of myeloma, a lot of the seeds that lead to myeloma, are there. We can detect abnormal protein levels and usually antibody levels, the same as in myeloma. But the major difference is that there isn’t any end-organ disease yet.

In myeloma, typically the classic criteria that we talk about are the CRAB criteria: calcium being elevated, renal function (meaning that the kidney function is decreased), anemia (which means low red blood cell counts), and bone disease. Bone disease could be punched-out lesions of the bone, which we call lytic lesions and which you can see on an x-ray or a CT scan or sometimes an MRI, or this can refer to actual fractures. Those have been the classic criteria that define myeloma.

In recent years, there's been an expansion of those criteria, where a patient normally would have been classified as having had the precursor condition, but there's just so much disease present that it's just a matter of time before they are going to develop myeloma. And so, we say, we might as well treat those patients earlier and get the ball rolling so that we don't run into those problems that we see with myeloma.

So, the thought is that every patient goes through these stages, but the difference is that some patients will know that they have the precursor condition ahead of time

because of some testing or some blood work that led to that evaluation. But other times, we don't know that they ever had it until we find out they have myeloma.

So, it's impossible for us to know when somebody transitioned to myeloma in some cases, unless we were watching it happen in front of our eyes. But typically, I'd say that these things are going on for years, sometimes even a decade or longer, before they develop into myeloma.

Mary DeRome (MMRF): Sarah, are there any specific side effects or symptoms that accompany a diagnosis of a myeloma precursor condition? Or, to put it in a different way, how does having MGUS or smoldering myeloma affect a patient's quality of life, and how does it affect a patient's body?

Sarah A. Major, PA-C, MMS, MPH: As Dr. Derman discussed, these precursor conditions, MGUS or smoldering myeloma, are, a lot of times, identified by changes in the blood work and some low-level involvement in the marrow, and the patients don't have any symptoms. They may not know, except that it's been picked up on their bloodwork. And that's because we haven't gotten to that end-organ damage point yet that would classify them as having active myeloma. They will have to get their labs monitored periodically. There is a psychological component to that; maybe they worry about the disease changing or progressing. But they are typically asymptomatic.

Mary DeRome (MMRF): Dr. Derman, our patient and caregiver audience has heard on many of our webinars about a possible familial connection with MGUS and smoldering myeloma and about the availability of some observational trials and testing. In your opinion, is it necessary for immediate family members of myeloma patients to be tested for a precursor condition so that it could be caught earlier? Would that be helpful?

Benjamin A. Derman, MD: It's a great question. It's something that comes up a lot. Previously, we thought that myeloma was not at all related to other cancers in families, that it's not something inherited or something that you'd get from mom or dad, but we're finding out that there is a small minority of cases that do seem to run in families, and it's not necessarily that you only see myeloma. It could be other blood cancers, like lymphoma or leukemia, or solid cancers like breast cancer or prostate cancer. It comes down to a case-by-case basis. For every patient I meet, the number one thing I'm looking at is their age and seeing if they got myeloma earlier than expected; that is one reason why I might be interested to know if they have a predisposition to develop a cancer, myeloma in particular. We think about 10% of myelomas are familial.

But I also look at family history, doing a deep dive, knowing about mom, dad, brothers, sisters, even, God forbid, children, who have cancers. And as you peel back the onion, sometimes you find there are good number of cancers in a family. And so, at the University of Chicago, we do a lot of genetic testing of our patients, both as a clinical and as a research interest for us.

The thing is, we can only find what we can look for. Part of the challenge with myeloma is that there may be mutations or genetic predispositions that are yet to be identified.

So, I am always in support of research efforts to further clarify this. The Promise study is probably the furthest along. Family members of people who have myeloma or other blood cancers and/or people who are African American can enroll in this study. But we're not there yet. We don't really understand what the implications are. Research is going to be the way to answer those questions.

Mary DeRome (MMRF): Absolutely. In some of the more recent meetings, they've been talking a lot about the iStopMM study that's going on in Iceland, where they're screening a large proportion of people who live in Iceland for precursor conditions. I think a lot of interesting population data are going to come out of that as time goes on. There are already some really interesting data coming out of that study. As you mentioned, research is key in answering these questions.

Benjamin A. Derman, MD: Absolutely. And I think it comes down to a few factors. Some patients want to know everything that's going on with their body, and they are of the mindset that they can handle that. But for other patients, it causes some emotional distress to know that they have a precursor condition that needs to be monitored, even though it may not affect them in their lifetime.

That's actually one of the things that they're investigating in the iStopMM, looking at the broad population. It's a beautiful study. It's going to give us tons of information. I don't know how applicable it will be to a U.S. population. I work in the South Side of Chicago with Sarah, and we take care of a lot of African American patients who have two to three times the rate of MGUS and smoldering myeloma and myeloma. We're not sure how much of the iStopMM data is going to be applicable to a U.S. population, but nonetheless, these are really important data.

Mary DeRome (MMRF): I agree. Julia, can you walk us through how you learned you had myeloma? For example, what led you to go to the doctor? Was it a symptom that you were experiencing, or did you have a strange result on a blood test during a routine exam?

Julia Grosch: I was diagnosed with multiple myeloma in May 2021. I had no symptoms that I would have attributed to multiple myeloma. I had a broken bone in my right foot in December 2020. Then I broke a bone in my left foot in February 2021, which led me to an orthopedic doctor, and he ran extensive blood work to make sure that there was no underlying condition, and the results came back with some concerns, which led to further testing and then a diagnosis.

Mary DeRome (MMRF): Got it. Yes, broken bones are common for patients when they first get diagnosed. Although, normally, it's broken bones in backs or shoulders; I haven't heard about a foot. That's a new one.

Julia Grosch: Yes, it was new to me too.

Mary DeRome (MMRF): Sarah, what information is important for patients and their caregivers to keep track of once their diagnosis with myeloma is confirmed?

Sarah A. Major, PA-C, MMS, MPH: This is a great question. When patients are first diagnosed, it can be very overwhelming. They're given a lot of information very quickly. So, it's helpful to have some things that they can focus on. First, it's important for patients and caregivers to take their time to understand everything that's happening, to be active during visits, and to be involved in the treatment plan, and not to be afraid to ask lots of questions, because repetition is key.

It's hard to understand everything the first time you hear it, so asking questions over and over to make sure that you understand is important. I encourage patients to keep journals so that they can write questions or notes from the visits to help them keep track of things that are discussed. Also, it is important to monitor how you're feeling, whether you have any symptoms or not, and whether you develop new symptoms or changes to your symptoms. This is very important for the patients and also for the providers, when the patient is diagnosed and starting on treatment.

It is also important to keep track of helpful handouts, information on your diagnosis, the chemotherapy regimen that they're planning, and supportive medications. It's helpful to keep all this information somewhere that's handy and where you know you won't lose it. It's very helpful to keep these things handy.

And with the lab markers that we're monitoring, it's helpful for some patients to follow these, but some aren't as interested in the labs. It is up to the providers to review these with the patients during visits and to help them interpret the lab results in a way that makes sense. We give our patients a lot of resources that explain the labs, what to look for, and what to monitor. Some patients just prefer to have us explain things to them.

Mary DeRome (MMRF): Yes. This is such a complicated cancer compared to some other cancers. There are, at least, some easily followed lab benchmarks that help track what’s going on, right?

Dr. Derman, speaking of complication, can you explain the process of risk assessment for a patient who is diagnosed with myeloma? We hear the term “standard risk” and “high risk” a lot. What do these terms mean? I think that there is still some ongoing discussion about this and what exactly is “high risk.” Tell us your opinion.

Benjamin A. Derman, MD: We can look at three different compartments, so to speak, when we're talking about myeloma. One is peripheral blood, which is the blood test that we take. One is in the bone marrow, which is looking at characteristics of the myeloma cells that are living in the bone marrow, because that's where they like to go to. And then you can do imaging, which includes things like CT scans, PET scans, and MRI.

Those are three different ways to keep track of the myeloma. When we talk about risk assessment, we're focused either on the peripheral blood or on the bone marrow.

Many years ago, physicians came up with the International Staging System (ISS), which is a very simple and easy-to-perform staging system. We have three stages: I, II, and III (there is not a stage IV in myeloma), and all it requires is two blood tests. One is an albumin test, which is a test of a protein that is present in the blood and can be low in higher-risk disease states. The other is the beta-2 microglobulin test, which is a blood test that is not used for diagnosis, but typically, the higher the results of that blood test, the higher the stage. Even those two simple tests can stratify patients into three groups: those who will be more responsive to therapy and will have a long-lasting response to therapy, versus those who are likely to have multiple relapses in short succession.

Since then, we've learned that chromosomal abnormalities in the myeloma cells that are in the bone marrow can add to that as well. This was clarified in the 2000s, when we found that there were mutations that signified patients who were likely to have early relapses. These include things like deletion 17p and the swapping of chromosomal material (called translocation) between chromosomes 4 and 14, between chromosomes 14 and 16, or between chromosomes 14 and 20. And recently, chromosome 1 has gained some attention: having extra copies of the long arm of chromosome 1 might be a bad prognostic sign, meaning that having those extra copies might indicate that a patient is more likely to have early relapse.

These tests may be helpful upfront because some physicians, including myself, may alter their treatment recommendations based on the test results. This might mean intensifying the induction therapy, which is the initial therapy that we give to patients. It might mean advocating more strongly for a stem cell transplant. It might mean more therapy after transplant. Some doctors don't use those tests to guide their treatment, because there is not overwhelming evidence to support the idea that changing the treatment is going to change the outcome. So, there's some disagreement about the utility of high-risk disease classification. And now we've gotten even more complicated with it, where we can actually look at specific genes and say that a specific gene mutation means that there is higher risk.

The field is evolving, and the better the tools that we have, the more we're going to be able to figure out which patients are going to do really well. The last thing I'll say about it is that, as some colleagues have told me, myelomas are like people: they have different personalities. Just like people, they give a first impression. So, sometimes a patient may have high-risk features, which would be a bad first impression, but then you find out that they responded well to treatment, and everything went fine. It also goes the other way: patients may have standard-risk features, and then you find out they didn't respond that way. A lot of what we learn about the myeloma happens early, in those first couple of years, and then we know what we're dealing with.

Mary DeRome (MMRF): That makes sense. Julia, can you tell us how you were able to become educated on multiple myeloma so that you could understand your lab reports

and other aspects of your care? I imagine that Dr. Derman and Sarah were instrumental in teaching you about this.

Julia Grosch: Oh, yes. After I was diagnosed and I processed the whole thing, I did go to several sites on the web, but I didn't want to do that too much, because I didn't know enough about it and I didn't want to misinterpret anything.

As Dr. Derman said, everybody's disease is different. I relied heavily on my medical team, Sarah and Dr. Derman, to educate me on my particular myeloma. As far as blood tests, again, I didn't want to misinterpret anything. The most extensive blood tests I'd ever had in my life were my LDL and my HDL. I knew how to interpret those. About these other blood tests, I had no clue, so I relied heavily on Sarah and Dr. Derman to help me through the whole process.

Mary DeRome (MMRF): That is great. I think it’s important to go to a major medical center for myeloma care and to talk to a specialist who is adept at treating myeloma patients and who treats a lot of them, because these are the physicians that are going to know the most effective and newest treatments. The problem is that not everybody lives near a center like that.

Dr. Derman, if a patient does not live within easy traveling distance to a major medical center with a great myeloma specialist, can they get good care at their local healthcare center?

Benjamin A. Derman, MD: Absolutely. I am a little biased, but I do think that being able to go to an academic center or to a physician who has expertise in myeloma is helpful. There is one study that showed that patients who are seen at academic medical centers for myeloma have better outcomes.

But that's probably a somewhat narrow-minded view. We work with a lot of community providers, and patients do get really good care from their community providers, even though they're not experts in myeloma. One of the beauties of the therapies for myeloma is that they are exceedingly well tolerated by patients. They preserve quality of life. In fact, they improve quality of life. So, they are easy to give in the community.

However, when it comes to understanding whether something like a stem cell transplant may be beneficial, that's not something that's necessarily going to be done in a smaller center. You would have to travel or do something like that. The advent of digital engagement has been a blessing. There's nothing to stop a patient from setting up a virtual visit, at least to start, though maybe it doesn't beat meeting your physician in person, because there's a lot that gets lost. But you can get a feel for somebody's personality and for the therapeutic relationship and get the information that you need from a trusted source. That's always an option. And your treating physician should have relationships with physicians in the academic centers, if you're in a small, rural, or distant community, to be able to provide you with information and contacts.

Mary DeRome (MMRF): I agree that the ability for patients to have virtual visits with physicians, nurse practitioners, or other healthcare providers has been game changing for a lot of people, which is a great thing. If the pandemic did nothing else, it did that for us.

Let's talk now about initial treatment for patients. Sarah, can you talk to us about what induction therapy is, how many weeks are in a cycle of induction therapy, and how many months, on average, induction therapy lasts?

Sarah A. Major, PA-C, MMS, MPH: Yes. Induction therapy typically starts with either a three- or four-drug chemotherapy regimen. This can be a combination of a few different drugs. Commonly, Revlimid (lenalidomide is the generic name) is used in combination with either bortezomib (Velcade), carfilzomib (Kyprolis), or daratumumab (Darzalex)

The choice of combination is commonly based on the patient's risk features, as Dr. Derman discussed. Often, a patient has chronic comorbidities or other medical conditions that might be affected by the chemotherapy drugs. We take all this into account when we decide on a treatment plan.

Typically, each cycle is about four weeks, and we typically complete about four to six cycles, so, it would last about four to six months, depending on the response. Then, we tend to reassess the disease response, and that helps us to decide next steps, whether it be proceeding with a transplant or extended chemotherapy.

Mary DeRome (MMRF): After those four to six cycles is probably when you would collect stem cells from patients before transplant? Or, even if they elected to delay transplant, you would still collect cells at that time, right?

Sarah A. Major, PA-C, MMS, MPH: Yes. We try to collect cells on most patients either way, even if they're a questionable transplant candidate, because it's the best time to do so, and then we have the cells saved for forever, if they are needed down the road.

Benjamin A. Derman, MD: The main reason for that is that the more chemotherapy you receive, the harder it is to collect stem cells, specifically when it comes to lenalidomide (Revlimid). That's one of the drugs where, it's a wonderful drug for treating myeloma, but it does make stem cell collection harder. And so waiting to collect the stem cells is not always a great idea, even if you don't want to proceed with the transplant right away.

Mary DeRome (MMRF): Right. Dr. Derman, many in our audience have heard about the results of the GRIFFIN study, comparing four-drug induction regimens to three-drug induction regimens, specifically Revlimid, Velcade, and dexamethasone, with or without Darzalex added to that combination. The results do show a benefit to the four-drug regimen. Is this becoming a standard of care for patients who are newly diagnosed?

Benjamin A. Derman, MD: Depending on whom you ask, you might get different answers. The analogy I use is this: imagine the new iPhone is coming out, and some people are in line the first day it's out. They want to get the new technology; they think it's going to make their life a lot better. Other people say, “I'm going to let people work out the bugs first, and then if it looks good, I'll hop on.” That is the situation we're in right now. We have some good preliminary data that show that adding daratumumab (Darzalex) to the standard bortezomib (Velcade), lenalidomide (Revlimid), dexamethasone combination leads to deeper responses, and we think it is likely to keep people alive longer without their disease progressing, which we call progression-free survival.

The two best things to know would be: One, does adding this drug in the beginning help you live longer and live better? We don't have a definitive answer to that question. So, what it comes down to, for clinicians and for patients, is the question of do you want to be the early adopter or not? I have been an early adopter of adding daratumumab (Darzalex). It is a very effective drug, and it doesn't cause a lot of side effects. So, that's been great.

The other thing is, I think we're going to find that this regimen is better for patients in the long run. We had these same discussions about adding Velcade to Revlimid plus dexamethasone. It took many years, and only recently did we get the definitive answer, but we've been using it for a long time.

The bottom line is, yes, for me, I would say it is a standard of my care, but I don't think that it's necessarily wrong to use the three drugs. In part, it comes down to the conversation that a patient has with their providers and determining what is right for them.

Mary DeRome (MMRF): I certainly have heard different things from different people. Some physicians say, “Anybody who is newly diagnosed gets four drugs from me.” But that's not the feeling from everyone.

Julia, what initial treatment did you receive? Can you tell us what you went through and how your care was coordinated?

Julia Grosch: My initial treatment was the three drugs. We started with Revlimid, dexamethasone, and Velcade. I think I might have done only one cycle of that, and then Dr. Derman recommended adding the fourth drug, Darzalex, and he said that it could possibly “clean up my system,” as he called it, so we added that.

My initial treatments were done at my local hospital, Central DuPage Hospital. The oncologist there worked in conjunction with the University of Chicago and Dr. Derman. Because I was going weekly, it was extremely convenient, because it was 30 minutes down the road. When it came to additional care after my initial treatment and stem cell transplant of course I went to the University of Chicago, but initially it was the three drugs, and then I went to the fourth drug.

Mary DeRome (MMRF): Sarah, lot of people have a trouble with dexamethasone. What are the ways that the side effects can be managed?

Sarah A. Major, PA-C, MMS, MPH: Yes. A lot of patients either love dexamethasone or hate it. On the one hand, it can provide some benefits. It can help a lot with pain, especially early in diagnosis. It can give patients some energy and it can help with their appetite if they have a poor appetite. But there are a lot of negative side effects as well. Most commonly, patients can experience difficulty sleeping (insomnia). They may have worsened fatigue as they "crash" when they come off the dexamethasone. And it can cause weight gain as well as increased appetite. It can cause high blood sugar levels.

This is especially important in patients with diabetes. We have to monitor them very closely when they're on dexamethasone, because it can wreak havoc with their blood sugar levels. If they are on diabetic medications, we have to monitor that closely, and a lot of times we might need to adjust those medications or add medications.

Other common issues are mood changes. It can cause increased irritability, frustration, and significant mood swings, and there are some gastrointestinal side effects, commonly abdominal pain, gas, bloating, constipation, and diarrhea.

The best way to manage a lot of these side effects is to quickly adjust the dose of dexamethasone, so we often quickly reduce the dexamethasone dose. We often start on a lower dose for patients that we know might be at risk for high blood sugar levels or something like that, because that can really make a big difference in patients' side effects. And we can drop it down pretty low to help with that. After the initial cycles, it's quite reasonable to do that. We also have supportive medications for gastrointestinal side effects or to help with sleep and other things.

Mary DeRome (MMRF): Dr. Derman, after a stem cell transplant, many in our audience hear about more treatment being given, and they hear the terms "consolidation" and "maintenance therapy." Are these the same thing?

Benjamin A. Derman, MD: Great question. Some of this comes down to semantics, to some extent, but think of it as stages. At the beginning, we have induction therapy; we're inducing a response. Some people will use the term "remission," but because we think that myeloma often can come back, we don't always use the term "remission." We say "response." Either way, we induce a response, and then we have transplant, and then after transplant, we're talking about one or two different phases.

The bottom line is that you are referring to treatment that is given after transplant. For some people, if you're giving one drug alone right after transplant, we call that maintenance therapy, and that's usually lenalidomide for most patients. When we talk about consolidation, that refers to multiple drugs or multi-drug maintenance therapy.

Some patients may get daratumumab afterwards, some patients may get bortezomib afterward, or carfilzomib. "Consolidation" refers to sometimes short, sometimes longer,

courses of therapy right after transplant. For instance, in the GRIFFIN study that you mentioned, which was a regimen of daratumumab plus Revlimid, Velcade, and dexamethasone prior to transplant, patients then got two cycles of consolidation, right after transplant, with those same drugs, and then they continued as maintenance therapy with Revlimid and daratumumab. That's an example where you have a consolidation phase and a maintenance phase as well.

Mary DeRome (MMRF): And that would be considered a line of therapy, right? So, induction, then transplant, then you may or may not have consolidation, and then most people have maintenance, but that's all considered to be one line of therapy, right?

Benjamin A. Derman, MD: Yes. It certainly doesn't feel like that to the patient; it feels like an endless stream of busy-ness. But the term “line of therapy” is important when we're talking about some later-line therapies. For chimeric antigen receptor (CAR) T-cell therapy, the FDA has said you need to have four prior lines of therapy before receiving CAR T-cell therapy. Certain clinical trials require you to have had a certain number of prior lines of therapy. That's why it's relevant.

Mary DeRome (MMRF): Along those same lines, Dr. Derman, most newly diagnosed patients are faced with a decision of whether or not to have an autologous stem cell transplant as part of their care. And we know from the DETERMINATION study that when to get a transplant, either as part of initial therapy or maybe after relapse from initial therapy, is one of the main issues that people think about. Is there any reason not to get a transplant following induction therapy? Are there certain situations in which delaying a transplant until after relapse from first-line therapy would be in the best interest of a patient?

Benjamin A. Derman, MD: I think this is a discussion that Julia and I had. During the older studies that looked at whether a transplant helped or not, those patients were not getting the same therapies (like bortezomib and lenalidomide) that our patients are getting now. What you're seeing in the more modern studies is that when patients get contemporary therapies, the benefit of transplant is starting to slip a little. It’s not as big of a difference as what we saw before.

Mary DeRome (MMRF): Yes. Back then, that was all people had.

Benjamin A. Derman, MD: Correct. And when I say the “differences in benefits,” you already said that we should be focused on whether patients are living longer or living better. In the two studies that have been done, one in France, one in the United States, they looked at just giving Velcade, Revlimid, and dexamethasone for eight cycles followed by lenalidomide maintenance, versus a transplant sandwich (Velcade, Revlimid, and dexamethasone, followed by transplant, followed by Velcade, Revlimid, and dexamethasone again), and then maintenance therapy.

In both studies, the overall survival at four, six, and eight years was similar. Meaning, the number of people who were alive four, six, and eight years out was similar between

treatment groups. Some people are going to argue, “Hold on a minute. Myeloma patients are living a long time, a decade or longer for even the average patient. So, you need to wait longer in order to see differences.” And they might be right. The number that we look at is called “progression-free survival,” which is not just the time that patients are alive, but the time during which their disease has stayed away. The idea being that if we can keep the disease from coming back for longer, that likely means it's going to help the patient live longer. And if we assume that is true, then when we look at transplant in the front-line setting, so to speak, that does help keep the disease from coming back for longer by a year or more.

That's something that is important to discuss with patients. A lot of it does come down to a more nuanced discussion, and for me, it's about meeting patients where they're at.

The last thing I'll say that is somebody here mentioned a cure for myeloma. I am unapologetically a believer that we can cure myeloma for some patients, and probably the best chance of doing that is getting an early, deep response. Your first shot is your best shot. Eight years out from a transplant, in the French IFM 2009 study, 35% of patients who got a transplant were alive and still had not had the disease come back. The result without transplant was down to 23%. It increases your chances of a long-term response by 50%, and I think that is important.

Mary DeRome (MMRF): Agreed. This is still greatly discussed. The DETERMINATION study just came out at the American Society of Clinical Oncology Annual Meeting this past year. So, it's been less than a year since those results came out. But it is very interesting.

Sarah, can you talk to us about how response to treatment is measured? Does it depend on the M protein level or light chain levels when you begin treatment? Is this measured in the blood, or is bone marrow biopsy required too?

Sarah A. Major, PA-C, MMS, MPH: It is a combination. The main thing we are looking for is the M protein or the “M spike level,” as providers may refer to it. It's measured by a serum protein electrophoresis (SPEP) lab. That's typically how we monitor most types of disease. For patients who have “light chain disease,” that is, who primarily produce light chains, we will monitor either their kappa or lambda light chains, and this is done in the blood as well. Those patients will have elevated light chains at diagnosis, and we will monitor throughout the course of their treatment. It is helpful to monitor their immunoglobulins, which are in their bloodwork as well, and this can be a way to track their myeloma and also to monitor their immune system throughout their course of treatment. And we do utilize a 24-hour urine sample periodically to monitor their urine, especially for patients with light chain disease, because they can have protein show up in their urine.

It is important to know the baseline levels, because this will help us determine the response to treatment. We use that as a comparison, and we have different response criteria that will help us determine how much of a response they've gotten. A 50%

reduction in these values would indicate a partial response (PR). More than a 90% reduction would be a very good partial response (VGPR). A complete response (CR) would be that the M spike is undetectable in the blood and the light chains have normalized. Then, we use the bone marrow to confirm that response. That is the most sensitive way to determine the remaining myeloma involvement in the marrow.

That will help us determine if the patient has any residual disease, if they are minimal residual disease (MRD) negative or positive, because that will help us determine if they've achieved a stringent CR. The stringent CR, which is our best form of response, would be undetectable myeloma in the blood and then an MRD-negative bone marrow biopsy. We do utilize a PET scan as well. That is helpful, especially if patients have a history of PET-positive disease, to really confirm that CR.

Mary DeRome (MMRF): Julia, tell us about your response when you underwent your initial treatment. I believe you opted for a stem cell transplant. Can you tell us about your decision to undergo a transplant and what the process was like?

Julia Grosch: My initial response to treatment was very good. Before transplant, I had between 5% and 7% of disease left. At that time, I did choose to do a transplant because I felt that was the best course to get as much of the disease out of my body as possible and possibly have a longer positive outcome. It was a good decision, it turns out. But the transplant itself, I would say, is a non-event.

Prior to transplant is when everything takes place. You go in and they harvest your stem cells, which is a process that's done in the hospital, and a needle is put into each arm. One needle takes out the blood with the stem cells and puts it in this big whirring machine, and then the blood gets put back in the other arm. That can take anywhere from four to six hours, and it can take one to three days.

That is a bit of a process, in itself. You're allowed to bring people. My husband was with me, so that was nice, to pass the time and drink and eat and things like that. The transplant itself is after you harvest your stem cells. You go home for a week or so, and then I was checked into the hospital on a Wednesday, and I was given a final dose of really strong chemotherapy. They gave me a rest day, and then my transplant was on the Friday after.

They literally come into your hospital room, and they hang a bag or two of your stem cells, and they infuse them back into your arm. And there you go. Now it's time to get started rebuilding.

Mary DeRome (MMRF): It’s such an involved process, right? We had a podcast not long ago where we had four patients talking about their stem-cell transplants. One woman who had been diagnosed very young, in her 30s, had had two transplants, and it worked out well for her.

We did mention MRD. Dr. Derman, can you explain what MRD testing is and what the results mean for patients? To help illustrate for our audience, if a patient underwent induction therapy followed by stem cell transplant and then is currently on maintenance therapy, and their MRD tests showed seven myeloma cells out of a million bone marrow cells, would you consider that to be MRD positive or negative? What are the next steps for that patient?

Benjamin A. Derman, MD: MRD used to signify “minimal residual disease.” There's been a slight change to call it “measurable residual disease.” We're referring to the same thing in the sense that Dr. Christopher Hourigan, who does AML and focuses on MRD, says there's nothing minimal about minimal residual disease.

Perhaps that’s right, because what we're talking about is finding low levels of cancer cells. I think of it as a pool. One end of the pool is four feet deep, and the other end of the pool is eight feet deep. If I asked you to go and find something on the bottom of the pool, if you wanted to look in the four-foot-deep end, you might get lucky and find what you’re looking for, if that's where it was hiding. That's the equivalent of the low-level passes that we do when we do a bone marrow biopsy or blood test. Maybe we can pick a single abnormal myeloma cell out of thousands of cells. But MRD is referring to looking at hundreds of thousands, or in some cases, millions of cells, to be able to pick out the myeloma. That’s like going to the eight-foot-deep end. So, there are different grades that we can look at. Why is this important? One thing that we know for sure is that being MRD negative, meaning not having any detectable disease by your method of measurement, is associated with better outcomes: longer time before the disease comes back or longer overall survival.

It's a bit controversial right now. Clinicians will tell me, “Dr. Derman, I don't know what to do with that information. If somebody's MRD positive, or if somebody's MRD negative, what does that mean?” Because they're thinking that myeloma may not be curable or there’s not enough information for them to change their management.

What we're trying to figure out, as a field, is, can we act upon these values? It's very rare to be MRD negative prior to transplant. Julia mentioned that she had 5% to 7% disease. That's more than MRD positive. That's something where even our pathologist can look at the bone marrow slides and say that there's something there. But after transplant per se, it gets to be very hard to pick up anything, and you may see nothing on the bone marrow.

What we found out is that not all CRs are complete. Patients who are MRD positive, meaning they have a low level of cancer cells detected by these more sensitive measurements, do about as well as those who still have detectable disease in their bone marrow at a higher level. That means that maybe we should be treating patients with MRD positive disease. Maybe more treatment is going to convert them. So, after transplant, for instance, maintenance therapy can convert some patients from MRD positive to MRD negative. Anywhere from 10% to 40%, depending on the study you look at. Even in the second year of maintenance, that can happen.

The trend is important too. A patient may have low levels of cancer cells, let's say it's 100 cells, but if it goes down to 30 cells in over a year, that's a good sign. A downward trend is good. Getting to complete negativity, to me, is a prerequisite for saying that someone may be cured. It doesn't mean that if you do it once, you're cured, but if you are seeing it consistently over time, it may be the case.

Ultimately, when we talk about discontinuing treatment, that is the situation where we might be able to do that. I'm running a trial right now where we're trying to answer that very question. I don't advocate stopping treatment just because you're MRD negative. But it could be a sign that we could do that, and knowing that information is helpful. But when somebody has a low levels, like 7, we would call that MRD positive at the 10^{-6} because there are seven cells per million. 10^{-5} refers to detecting between 10 and 99 cells per million. There are different grades that we can look at; basically, the lower the number, the better, and if we see increasing numbers, that typically is going to tell us that the disease is going to be coming back soon. I hope that helps clarify a bit.

Mary DeRome (MMRF): Thank you.

Sarah, sometimes patients have chronic health conditions along with their multiple myeloma, and we already talked about patients who may have diabetes and the effects that dexamethasone may have on people who have that disease. Patients also might have autoimmune diseases like lupus or rheumatoid arthritis. How do separate health conditions like these affect a patient's eligibility for a stem cell transplant? What drugs might be used in their therapy?

Sarah A. Major, PA-C, MMS, MPH: Certainly, we take all these factors into account when we're deciding what initial therapy to use, and then ultimately, whether the patient will be transplant eligible. And an important factor, too, is how well some of these conditions are currently controlled and managed.

For patients with preexisting neuropathy, we try to avoid using bortezomib (Velcade) in those patients, because that could make the neuropathy worse. For patients with cardiac conditions, we have to be careful with how we use, or if we use, carfilzomib (Kyprolis), because that can have some cardiac side effects. Depending on the condition, we still might be able to use it, but we'll need to monitor closely or adjust at lower doses. For transplant eligibility, we do take into account the severity and the number of other chronic health conditions that the patient has.

To help with this, we use our transplant optimization clinic, or our "TOP" clinic as we call it. Patients with a lot of comorbidities and older patients are sent to this clinic to get a risk assessment, and the clinic can recommend if patients can be optimized, potentially, for transplant. This really helps guide us, with these patients with more complex, chronic medical conditions.

Mary DeRome (MMRF): Great.

Sarah and Dr. Derman, I'm going to give you a series of questions that we've received from patients. I'd like you both to weigh in on some answers. First of all, do any myeloma treatments cause memory loss?

Benjamin A. Derman, MD: Typically, we think of lenalidomide or pomalidomide, which may be associated with memory loss. It's always hard to know definitively. I never make a clear diagnosis of that. In fact, I treat a lot of older adults, so some of this may be related to aging. But that is something that we have to keep in mind.

Mary DeRome (MMRF): Absolutely. Sarah, do you agree?

Sarah A. Major, PA-C, MMS, MPH: Yes, I agree.

Mary DeRome (MMRF): Sarah, you were talking about peripheral neuropathy, which is damage to the nerves, with Velcade. Patients find it very disturbing when they have these symptoms. I think that a lot of patients have it, but either they don't report it or there really isn't much that you can do about it. Does this neuropathy also affect the sensation of taste?

Sarah A. Major, PA-C, MMS, MPH: It can. I would say though, that's not the most common form that we see with the Velcade. A lot of times it's simple sensation changes in the feet or the hands, or the patient might not really know how to describe the sensation. That’s not to say that it can't cause some changes in their taste sensation. But I would say it's more the peripheral neuropathy that we see.

Mary DeRome (MMRF): Yes, which is more in the toes and fingers.

Sarah A. Major, PA-C, MMS, MPH: Yes.

Benjamin A. Derman, MD: Certainly, after a stem cell transplant, a patient may have a loss of taste for a period of time, and that's related to the chemotherapy.

Mary DeRome (MMRF): There are also myeloma patients who experience pain, and there's a lot of discussion in myeloma patients about the pain that they feel and about what is the cause of that pain. We had one patient write that they've been a patient for 15 months and they've never experienced any pain. Some other patients have experienced terrible pain. I think patients want to know, if they have no pain, is that a good sign or not. I think that, in general, pain is frequently how myeloma is diagnosed, and that can be related to broken bones or some other things. So, Dr. Derman, talk to us about pain.

Benjamin A. Derman, MD: Some of it comes down to the personality of the myeloma. Some myelomas affect the bones more. Others affect the kidneys more, or something else. Some people are diagnosed simply based on lab work and a bone marrow biopsy, and they're essentially asymptomatic. It doesn't necessarily mean a good thing or a bad thing if you have pain. Of course, we don't want people to be in pain, and if they have

significant bone disease, they're at risk for fractures. So, pain might be a sign that they fractured something.

But pain, in itself, is not a good or a bad sign from a prognosis standpoint. I often tell patients, if they're in a lot of pain, "Give us two months, and you're going to be a completely different person from the time that we start therapy." Often, you'll notice that pain dissipates just because you're killing cancer cells during that time. You're getting rid of the myeloma, which has gotten itself into the bone and caused these issues.

But there is a period, especially in the first couple of weeks of therapy, where patients are maybe at a slightly increased risk of fractures. You're not always out of the woods right after you start therapy, but if you give yourself about two months or so, it will be a completely different situation.

Mary DeRome (MMRF): Yes. And along those same lines, a lot of times, patients want to exercise after they start to feel great. At what point during therapy or after therapy are patients able to exercise? To go hiking, go biking, run, play tennis, and so on, and feel confident that their bones won't break?

Sarah A. Major, PA-C, MMS, MPH: Throughout their treatment course we do educate patients that they do have to continue to be careful even after the initial phase of treatment, with regards to higher-impact activities. And we do put a weight restriction of typically 10 pounds for our patients to avoid. Because they still, yes, will be at risk for fracture. But we do also encourage our patients to do some daily activity. As they go through their chemotherapy regimen, and they start to know how they feel and if they'll be able to perform certain activities, we do encourage them to slowly increase their activity, ideally with lightweight or low-impact activities such as walking. This will depend, too, on what they did before their diagnosis (their physical state, what their typical activities were). We advise them to be cautious throughout, but we do encourage activity as well.

Benjamin A. Derman, MD: I echo those sentiments exactly. Julia is a patient, for example, who's always been very active. Julia, when did you feel like you could be yourself again, in terms of your activity level?

Julia Grosch: I came home, and then probably two or three weeks later I started doing some low-impact exercise. I would hit the bicycle and my goal would be ten minutes, and then the next day would it be 15 minutes. I continued to lift weights, and I felt very comfortable doing most everything that I normally did in the past, after my transplant.

I'm back to my normal activities constantly and weightlifting, so everything is going well.

Mary DeRome (MMRF): Great.

On behalf of the MMRF, I'd like to thank Dr. Derman and Sarah Major and also Julie Grosch for joining me today. We had a great discussion. Thank you so much.