

FAQs on Multiple Myeloma Precursor Conditions

May 16, 2023

Transcript

Veronica Bohorquez (MMRF): Welcome and thank you for joining us for today's session, *Frequently Asked Questions on Multiple Myeloma Precursor Conditions*. I'm Veronica Bohorquez, manager of patient education at the Multiple Myeloma Research Foundation, filling in for Mary DeRome. I'm joined today by Dr. Shaji Kumar from the Mayo Clinic in Rochester, Minnesota. We've invited him to answer some of the frequently asked questions we receive from patients and caregivers about the precursor conditions monoclonal gammopathy of undetermined significance, or MGUS, and smoldering multiple myeloma.

Dr. Kumar, we're going to begin with a few questions focusing on diagnosis. We often hear about patients with MGUS or smoldering myeloma who have relatives that had myeloma or some other type of plasma cell disorder. Can you tell us what the familial link is between myeloma and its precursor conditions?

Shaji Kumar, MD: That's a great question, Veronica. This is something that always comes up in the clinic: "Are my relatives at an increased risk?" And we often hear about patients in the clinic who say, "My brother had it," or, "My aunt or uncle had it." What we know, from the studies that have been done, is that first-degree relatives of patients with myeloma or any of the plasma cell disorders have about two- to three-fourths' higher risk of getting a plasma cell disorder compared to the general population. Even though that appears to be a substantially higher risk, when you think about the overall frequency of these conditions, the absolute risk of your getting it is still far, far lower than the risk of getting a lot of other common clinical conditions that one might get during the lifetime. Why does it happen? We don't entirely know why. We have not been able to identify a particular genetic link that is inherited amongst family members.

It's quite possible that it's a combination of a genetic aspect as well as shared environmental exposures, such as growing up in the same household, being exposed to similar environmental agents, especially things like pesticides and petroleum products, all of which we know have been linked to an increased risk of getting plasma cell disorders. I suspect it's a combination of genetic and environmental factors. There is an increased predisposition within families, but again, I think it's important to highlight that this is very, very small in terms of absolute risk.

Veronica Bohorquez (MMRF): As a follow-up, for people that have a first-degree relative who has myeloma or one of these precursor conditions, are these individuals at higher risk of having a precursor condition? And should they be seeing their primary care doctor more often than normal, so that they can catch a diagnosis sooner?

Shaji Kumar, MD: That is a question that we are continuing to work on finding the answer for. Right now, to the question of whether a family member should be screened for monoclonal protein, given that it's a simple blood test, the simple answer is no. Because, again, we're talking about a condition that is relatively rare. Despite that increased risk, it remains a very, very low probability that a given person would have a monoclonal protein in their blood or urine.

Having said that, there are two important aspects of the monoclonal plasma cell disorders. One of them is the increased familial risk, and the second is the increased risk that we see in certain populations. We know that Black individuals have a two- to three-fourths' higher risk of getting monoclonal plasma cell disorders. If you're talking about a Black individual who has, let's say, two siblings who also have monoclonal gammopathy, that is a situation where we think we should screen by doing a blood test, because now you are multiplying that two- to three-fourths' higher risk by another two- to three-fourths' higher risk. It gets to a point where I think it's worth knowing if somebody has it. I think it's also important to note that, when you screen for something like this, the average age of an individual identified with a monoclonal protein is in the 60s, and we believe it probably starts somewhere in the 30s. So, it takes 15 to 20 or maybe 30 years to get to a point where it's large enough to be detected. So, if you do it very early, you may not even find it. It may be more applicable when you start screening people beyond age 50. In fact, we are looking at some studies, particularly using some of those very sensitive tests like the mass spectrometry-based testing for the monoclonal protein, to see if there is a particular age where we can screen and a negative test result might predict that person will never get a monoclonal plasma cell disorder during their lifetime.

Veronica Bohorquez (MMRF): That's a great segue into our next question. What is the difference between MGUS and smoldering myeloma?

Shaji Kumar, MD: Common to these is the fact that you have increased numbers of plasma cells that are dividing without the normal controls that are put in place. Typically, the plasma cells would multiply when exposed to an infectious agent or a foreign substance. They increase in number, take care of the issue, and then kind of whither away. But in the setting of these monoclonal cell disorders, you have a plasma cell or a set of plasma cells that continue to divide and continue to increase in number. It's a spectrum, starting at one end with what we call a monoclonal gammopathy of undetermined significance, MGUS: these plasma cells have increased in numbers, they do make some protein, but the percentage of the plasma cells is less than 10%, and the amount of M protein that they make, called the M spike, is typically less than 3 g. Now, at some point in time, they could cross those thresholds. Then, you have maybe 11% plasma cells or 12% plasma cells or 20%. Or you could have an M spike that is now 3.5 g, or light chain in the urine that is almost 500 mg or more over 24 hours. Once you've crossed those thresholds, now you call it smoldering multiple myeloma.

One might ask why we have this artificial line in sand, so to speak. Part of the reason why these definitions were created was because we know that if somebody has crossed

those thresholds and now are at the smoldering stage, their risk of progressing to active myeloma is much higher than somebody who has MGUS. Now, is the risk for somebody at 3.1 g much higher than that for somebody at 2.9 g? No, it's a gradual increase in risk, but we have to draw the line somewhere so that those patients can be put under closer surveillance, so that we pick up the progression as soon as it happens, rather than checking them less often, as we would do in the setting of MGUS. So that nomenclature of MGUS versus smoldering myeloma has been primarily put in place to decide how often do we need to follow up with somebody so that we can find it before it gets to be active myeloma.

Veronica Bohorquez (MMRF): Do you know what percentage of patients with MGUS or smoldering myeloma progress into multiple myeloma? Also, at what point is MGUS or smoldering myeloma considered myeloma?

Shaji Kumar, MD: Those are important questions. In terms of the risk of progression, when you look at the patients who have MGUS, their risk of progression is roughly 1% per year. It's a very interesting phenomenon because it's a very constant number. If you have 100 individuals with MGUS that you're following on an annual basis, every year, 1 patient out of that 100 would go on to get active myeloma, roughly. And this percentage doesn't really change over time. So, in about 30 years, if you've been watching those 100 people, approximately 25 of them would have gone on to get myeloma or something that's related. Now, there are certain characteristics within each individual — type of monoclonal protein, type of light chain — all those things can have an impact on that risk. But the average is 1% per year. In contrast, for those patients who have crossed those thresholds and now have a smoldering myeloma, the risk is different. If you take 100 people with smoldering myeloma that were diagnosed today, in the next five years, about 50 of those 100 people would have gone on to get active myeloma. And in 5 more years, another 15% may have gotten myeloma. But once you go beyond that 10- to 15-year mark, the risk of progression becomes almost 1% per year, just like the MGUS. This highlights something fundamental to these definitions, which is that smoldering myeloma is really not a distinct entity. You can think about it this way: you have myeloma or you have a precursor phase. That definition of “smoldering” was primarily created so that we can identify those people who have gotten closer and closer to myeloma, so that we can watch them much more closely. Typically, for a patient with MGUS, we would watch them once a year. Somebody with smoldering myeloma, we would watch them once every three months or so because of the increased risk. These are general guidelines. As I said before, somebody with an M-protein level of 3.1 g and somebody with 2.9 g, even though they are called different things, we might elect to watch them in a very similar fashion.

Veronica Bohorquez (MMRF): Is there a way to tell which MGUS or smoldering myeloma patients are at the highest risk of progression to multiple myeloma? And as a follow-up question, does the PANGEA model, which we recently heard about on our *Precursor Conditions with Updates* webinar, have anything to do with this?

Shaji Kumar, MD: Absolutely. Just to talk about what distinguishes active myeloma from smoldering myeloma, there have been criteria that have been developed to say who has active multiple myeloma. Before 2014, we relied on what we call CRAB features, which meant that a patient had high calcium levels, their kidney function had changed, they had developed anemia, or they had developed bone disease. We would like to catch people before they develop any of these clinical symptoms and signs, particularly bone disease, which puts individuals at risk for breaking the bone or having some catastrophic events like compression of the spinal cord, or the kidneys shutting down.

In 2014, we were able to identify some specific biomarkers that allowed us to predict who is going to get the CRAB features in the next couple of years. And those included people with a free light chain ratio that is over 100 (that is a blood test that you do in the blood, looking at the free light chain levels) or who have MRI-detected lesions (not bone that has been destroyed, but rather changes in the bone marrow). And obviously, if they have 60% or more plasma cells in the bone marrow. Any of those seven characteristics (the three that are picked up on testing and the four CRAB features) would identify somebody whose disease we would call active myeloma that needs treatment.

Going back to the risk factors, there's a bunch of different risk factors that have been identified. Obviously, quantity is one of them. If you have a high M spike, high levels of free light chain, an abnormal free light chain ratio (whether it's kappa to lambda or lambda to kappa), or a high plasma cell percentage, all of this denotes, to some extent, something that has progressed: there is a lot more of those abnormal cells. But there are also characteristics that are more related to how bad these cells are. These characteristics would include what kind of genetic abnormalities these plasma cells carry, whether these patients have a larger number of these plasma cells in the bloodstream, and whether they are surpassing the normal immunoglobulins; all those things can also impact the risk of progression.

What has been attempted over the years is to develop scoring systems that would give a specific score to a given scenario or a given patient to say, "Yes, your risk of getting myeloma in the next five years is X percentage." That's what has driven how closely we might follow the patient. The most commonly used risk-scoring system for smoldering myeloma is what we call the 20/2/20 staging system, which was originally developed at the Mayo Clinic and subsequently was validated, with a large cohort of patients, by the International Myeloma Working Group. That model was developed primarily with smoldering myeloma patients and is primarily intended for use in smoldering myeloma. So, if somebody has a low score now, but they get a high score a year later, the risk of progression would have gone up at that point in time. This system is something that can be used multiple times, over years.

What do the numbers mean? The 20/2/20 stands for 20% plasma cells in the bone marrow or more, more than 2 g of M spike, and a free light chain ratio that's more than 20. If you have two of those three characteristics, then your risk of developing myeloma is roughly 50% in the next two years. Now, there is a more granular version of the same

20/2/20 system where, instead of just using 1 cutoff, we can use multiple different cutoffs to develop a score. That includes cytogenetic abnormalities that you see in the fluorescence in situ hybridization (FISH) testing. Then, you can have a score of up to 16. Any score over 12 denotes almost a 70% risk of progression 2 years from diagnosis. That gives you a more nuanced description; instead of just saying you have a risk of more than 50% at 2 years, we can say you have 20%, 40%, or 60% risk at 2 years or 5 years. It gives you more accurate numbers.

The PANGEA model was developed more recently, but that was developed primarily in a combined group of patients with MGUS and patients with smoldering myeloma. So it's hard to compare that model with the 20/2/20 model, and it cannot be applied in individual populations. It's something that is used for everyone that is "pre-myeloma," so to speak.

Veronica Bohorquez (MMRF): I see. Thank you, Dr. Kumar, for explaining the 20/2/20 criteria. To follow up on these criteria that are utilized in assessing risk, if a patient with smoldering myeloma falls under the 20/2/20 criteria, but has been stable for 10 years, is this considered low risk or not? That is, does the length of time someone has lived with their precursor condition factor into whether you would consider a clinical trial for treatment or not?

Shaji Kumar, MD: Absolutely. I think it's a very, very important point, because, as I said, smoldering myeloma is kind of a mixed bag of MGUS and active myeloma, and it takes us almost ten years to separate out those two from within that group. So, if you haven't progressed from the diagnosis of smoldering myeloma by ten years, your progression is almost the same as that of a MGUS patient. Once we get to that point, then we would consider maybe less intense follow-up. Initially, we would follow up every three months; maybe after five years, if nothing has changed, we can follow them every six months for the next five years. And if nothing has changed still, we could reduce the follow-up frequency to every year. Having said that, stability for ten years doesn't necessarily mean it cannot progress any more. Things can change, so I think less intense but still regular follow-up is important, to make sure that we don't miss out on these individuals progressing to myeloma.

Veronica Bohorquez (MMRF): Excellent. So, monitoring certainly plays a key role for patients with MGUS and smoldering myeloma. What can these patients with MGUS and smoldering myeloma expect regarding their care and follow-up after a diagnosis is confirmed?

Shaji Kumar, MD: With MGUS patients, the first thing we diagnose is monoclonal protein. We clearly want to check that in three to six months, to make sure that they didn't just capture a snapshot of something that was just continuing to go up. Once we can confirm that things are stable over three to six months, then, if they are an MGUS patient, we can follow up once a year. And even within the MGUS patients, there can be risk stratification, which tells us that for certain patients, the risk might be really low and that we could follow them maybe once every two to three years. And others may be at a

higher risk, and we follow them maybe every year. And that determination is based on some of these characteristics like the M spike size, the free light chain ratio, and so forth. Once the MGUS is identified, the first thing is to make sure the diagnosis is really, truly MGUS. Sometimes you can have patients with low levels of monoclonal protein who may have other associated conditions like light chain deposition, disease where the kidneys can be affected, or amyloidosis, which can affect a variety of different organs. We do want to make sure that none of those conditions exist at that point. Once we are convinced that this is truly MGUS, then it's a just matter of following them. There have been a lot of other disease associations that have been described. Sometimes people with MGUS can be at higher risk of getting infections or of developing osteoporosis. We don't know how strong these associations and how much of it is cause versus effect, and whether they are just associations that happened to go with age. I think it's important that the primary care physician ensures that the routine things that we do on an annual basis are continued. Obviously, if you have a smoldering myeloma, in addition to following all these markers much more closely, we always need to have an eye out for any clinical signs or symptoms that might indicate that the disease is progressing.

Veronica Bohorquez (MMRF): We're going to transition a little bit and talk about treatment and prevention with precursor conditions. Patients are sometimes surprised to hear that there is no need to treat MGUS or smoldering myeloma. Why is this the case?

Shaji Kumar, MD: It is more difficult to tell the patient with smoldering myeloma or MGUS that we are not going to do anything than to tell a myeloma patient that, "This is the treatment that they're going to give you." It's just human nature that when we identify something as wrong, we need to do something to fix it. But it's not just MGUS. We encounter this in a variety of hematological cancers, and even other cancers, too, prostate cancer, for example, where we know that a significant proportion of patients will never get to a point where the cancer is going to do any harm or shorten their life span.

And the treatments, at the same time, come with their own baggage of side effects. There is a real possibility that, if you were to take that example of 100 patients with MGUS, 70 of them will never get to a point where they need treatment for their MGUS. If you were to treat all 100 of those people, 70 people would have gotten treatment for no good reason, and these medications are not without side effects. It's always a balance between risk versus benefit. If tomorrow we would have a drug that would bring the M spike down with almost no side effects, then we could say, "Sure, let's treat all of those patients with MGUS." But that is not the case today, and the treatments we use for smoldering myeloma, for example, are often drugs that we use for treating myeloma and come with their own side effects. We want to make sure that we only give them to patients where the risk is high enough that the treatment provides a meaningful benefit. And that's where many of these risk scoring systems come into play, so that we can take those smoldering patients and say, "This is the 50% of the patients who are at a high risk of progression over the next 2 years; let's do something about it." Of course, we don't want to do that in the absence of any data supporting it. Thankfully, we have two large phase three trials that have shown that if you treat patients with high-risk

smoldering myeloma with either a drug like lenalidomide (Revlimid) or lenalidomide with dexamethasone, you can not only delay the time it takes for people to develop myeloma, but also, as the Spanish trial has shown us, people actually do live longer. Obviously, there are lots of ongoing trials answering a variety of questions that we don't know the answers to: In addition to just treating these people, what should be the treatment? Should the treatment be based on their underlying risk? So that, for somebody who is much closer to myeloma, maybe we treat them like they have myeloma. And somebody who is closer to MGUS, maybe we treat them with something much less intense.

Veronica Bohorquez (MMRF): I think that turns us to our next question. As patients are being as active as possible with this diagnosis, are there any signs or symptoms that patients with MGUS or smoldering myeloma should be sure to mention to their doctors, things that might be relevant to their disease or possibly a sign of progression? For example, many patients with smoldering myeloma ask if having osteoporosis is a CRAB feature of myeloma.

Shaji Kumar, MD: Osteoporosis, per se, is not a CRAB feature, because you can have osteoporosis that's just associated with age. If we have a 70-year-old individual with some osteoporosis, we won't worry as much that the plasma cells or the MGUS or the smoldering myeloma is responsible. However, if we have a 45-year-old with significant osteoporosis, then we worry that plasma cells are really doing some damage. But typically, when we talk about bone disease, we are talking about lytic lesions, which are basically holes in the bone that are created by these collections of plasma cells eating away at the bone. In terms of symptoms, the general principle that I always tell patients is, if you develop a symptom that is unusual and doesn't go away, make sure you tell your physician to have it evaluated. But the typical things that we would worry about are bone pains, frequent infections, a fracture with very little trauma, or somebody becoming anemic. Or, you know, it's not just myeloma, right? Some people can develop amyloidosis. If you start getting short of breath, if you start having swelling in the feet, or if you start bruising easily, or having numbness and tingling in your fingertips or toes indicating neuropathy, all those things could indicate that the underlying plasma cells are doing mischief, but do not necessarily fall into that bucket of myeloma.

Veronica Bohorquez (MMRF): Excellent. These are helpful things for patients to consider as they're navigating. Dr. Kumar, following up on the topic of treatment, if the rationale for not treating patients with MGUS or smoldering myeloma is to spare them the potential side effects of treatment, what are some specific side effects that come with starting myeloma drugs early? Can you describe what these potential side effects are?

Shaji Kumar, MD: Absolutely. Of course it depends on what type of treatment we use. If you are talking about commonly used drugs, or combinations of two, three, or four drugs, in a patient with newly diagnosed myeloma, then we are talking about a monoclonal antibody like daratumumab (Darzalex) and medications like lenalidomide, bortezomib (Velvade), and dexamethasone. With daratumumab, there can be infusion

reactions associated with it. It does suppress your immune system, to some extent, and increase the risk of infections, especially if given over a long period of time. It can be associated with quite a bit of fatigue in some patients. Lenalidomide can be associated with a drop in blood counts, it can cause increased risk of blood clots, and long-term treatment with might be associated with an increased risk of getting other cancers. You can also have chronic gastrointestinal disturbances like diarrhea associated with long-term lenalidomide therapy. With bortezomib, you can develop peripheral neuropathy. It can also increase your risk of infections, and it can drop palatal counts, often just transiently. And dexamethasone, also, can increase the risk of infections, weight gain, difficulty sleeping, and so forth. These are the major side effects, but all of these drugs can be associated with much rarer side effects, as well.

Veronica Bohorquez (MMRF): Most of our patients are very focused on treatment, but of course this does not necessarily mean that treatment is always applied. However, if patients are just monitored over time for signs of progression and do not receive any treatment, are there any data to support a certain diet or lifestyle that may be of help in preventing progression to myeloma?

Shaji Kumar, MD: That is a question that comes up all the time. We don't have anything that has been scientifically proven to slow down the rate of progression, neither diet nor exercise. Having said that, I think it's important to have a good healthy diet and also make sure there's plenty of exercise as part of your daily routine. Because these are not specific to MGUS. These are things that will be good for a variety of different conditions and overall health and longevity in general.

Veronica Bohorquez (MMRF): We're almost at the end of our conversation. As a concluding thought, I'd like to ask you this final question. How best can patients with MGUS or smoldering myeloma cope with their diagnosis? It has to be very stressful knowing that you have a disease that may eventually progress to multiple myeloma, but at this time, there is no treatment outside of a clinical trial.

Shaji Kumar, MD: Yes, it is always the most challenging discussion that we have. It's hard to tell someone that there's a sword hanging over their head but we just don't know when it's going to fall. But I think that understanding the actual risk and the probability that they may never end up in that situation is the first important step. The second important step, I think, is having the reassurance that we're going to be watching it closely. We can never say with 100% certainty that we'll be able to catch everything on time, but it's close to that, and it is likely that we'll be able to identify when things are getting bad. The other aspect of reassurance is that, even if it does get to a condition like multiple myeloma, we have so many new drugs that are so effective in controlling this that the myeloma itself is starting to be no longer the death sentence that it was a long time ago. It is something that we can actually treat. And hopefully, in the coming years, we will be able to confidently say that it's more of a chronic disease rather than a fatal cancer.

Veronica Bohorquez (MMRF): Thank you, Dr. Kumar, for your time today. On behalf of the MMRF, I'd like to thank Dr. Kumar for joining us today and for his great, detailed answers to our questions. If you have any additional questions, please call our MMRF Patient Navigation Center at 1-888-841-6673.