FAQs on High-Risk Disease

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Transcript

Mary DeRome (MMRF): Welcome and thank you for joining us for today's session of Frequently Asked Questions on High-Risk Disease. I'm Mary DeRome, Senior Director of Medical Communications and Education at the Multiple Myeloma Research Foundation. Today I am joined by Dr. Jonathan Kaufman and Sara DiCamillo from the Winship Cancer Institute at Emory University in Atlanta, Georgia, and Steve Hoofnagle, a myeloma patient living in Atlanta, Georgia. They have agreed to answer some common questions that patients or their caregivers have about high-risk disease.

We often receive questions about high-risk multiple myeloma. Dr. Kaufman, my first question is for you. With regard to multiple myeloma, what makes someone's disease high-risk? And how does that impact their prognosis?

Jonathan Kaufman, MD: First, hello to everybody. And hi, Mary.

In large part, high-risk disease is defined by what we call either “cytogenetic” or “FISH” (fluorescence in situ hybridization) abnormalities inside of the myeloma cell. There are typical abnormalities that we see in the genetics or in the chromosomes of a myeloma cell that confer high risk. The genetic abnormalities that are typically considered high risk are deletion of what's called 17p. That's the small part of chromosome 17. There are what we call “translocations” that are considered high risk, where translocation means a part of one chromosome is mixed and matched with a part of another chromosome. So, for example, for the (4;14) translocation, part of chromosome 4 and part of chromosome 14 are mixed and matched. We'll say “t(4;14),” and that confers high risk. There’s also a translocation (14;16).

And then, some of the more recently identified high-risk features are abnormalities of the chromosome 1, a gain of 1q and a loss of 1p. Those are considered high-risk abnormalities. And just for some clarification, when I say "q," that's the longer side of the chromosome, and “p” is the smaller side of the chromosome. And we have a test called FISH, which seeks out these areas within the myeloma cells to determine if a patient has these abnormalities.

And so, to answer the second part of your question, what does it mean when I say high risk? Basically, our approach is to classify patients broadly into two groups: standard risk and high risk. What high risk means is that an individual patient is at higher risk for the myeloma coming back earlier after initial therapy and higher risk of dying earlier from myeloma compared to the standard-risk

patient. That's the easiest way to understand risk. And so, we have some things that we do differently because a patient has high-risk disease.

Mary DeRome (MMRF): This has been sort of an evolving conversation over the past number of years in the myeloma field, and I think that we're getting pretty close to a consensus now as far as what high risk is and what to do about it.

And many of the clinical trials that are ongoing will delineate the activity of an agent in the high-risk population versus in the standard-risk population of patients, which I think is useful if you're one of these high-risk patients. It's good to see that there's been so much attention paid to this, because it's a fairly important facet of people's disease, whether or not they're high risk. And it definitely matters.

Sara, can a person's risk status change throughout their myeloma? In other words, can a patient go, for example, from being a standard-risk patient when they're first diagnosed to a high-risk patient farther down the line? Or vice versa?

Sara DiCamillo: Hi, everyone, and thanks, Mary, for having us. For this question, as Dr. Kaufman mentioned, we like to assess risk at diagnosis, early on.

And when a patient is fit into the high-risk category at diagnosis, they'll always be considered a high-risk patient. Those patients will not transition to a standard-risk situation.

Conversely, on the other side, patients can have standard-risk disease at diagnosis and later, during relapse, might develop some high-risk features. As examples of this, if a patient relapses early in the first couple of years, we consider these patients to be functionally high risk. Also, when patients relapse, we might do a bone marrow biopsy and see new cytogenic abnormalities that were not present at diagnosis. Some of these Dr. Kaufman mentioned: deletion 17p, gain of 1q. Lastly, other things like plasma cell leukemia or extramedullary disease are other ways that patients can present with high-risk features. Again, this just tells us that the myeloma has changed to a more aggressive form and, unfortunately, usually with a poorer prognosis.

Mary DeRome (MMRF): So, Dr. Kaufman, myeloma patients undergo lots of different tests to characterize and monitor their disease. Sara just mentioned the bone marrow biopsy, which is an important part of that. What type of testing is done to determine a patient's risk status? And how often is that repeated?

Jonathan Kaufman, MD: As Sara mentioned, the most important time to understand a patient's risk is when they are newly diagnosed. That's the bone marrow biopsy. The standard test is looking at the cytogenetics and the FISH test. A bone marrow biopsy is definitely important for that.

The other important test in high-risk patients—and probably in all patients, but particularly in high-risk patients—is to do what's called a PET scan. A PET scan helps us to determine, for all patients, whether a patient has myeloma bone disease, but high-risk patients are more likely to have what's called EM or extramedullary myeloma, meaning that we see evidence of myeloma outside of the bones and bone marrow. When we say "medullary," we're talking about bones and bone marrow, and "extramedullary" means outside of the bone marrow. So, if we saw a tumor of myeloma or a plasmacytoma in an organ, or a lymph node that was full of myeloma, that would be considered extramedullary disease. Whether that happens early in the course or late in the course connotes a more aggressive or high-risk myeloma.

Mary DeRome (MMRF): So, what is the relationship between high-risk chromosomal abnormalities and the other laboratory values that also connote high risk, like beta-2 microglobulin or lactate dehydrogenase (LDH)?

Jonathan Kaufman, MD: The standard staging criteria for the higher stages, ISS (International Staging System) stage III or revised ISS stage III, include things like the beta-2 microglobulin. We're learning more and more that the major drivers of risk are really centered on the cytogenetics, because there can be high beta-2 microglobulin and high LDH driven by high-risk cytogenetics, but they’re somewhat nonspecific: we can see elevations of beta-2 microglobulin based on kidney function, and we can see elevations of LDH based on many things that aren't specifically related to myeloma. And so, I think the more we put our research together, the more we're homing in on the fact that it's really the cytogenetic abnormalities that drive everything.

I would say one of the challenges that we have in cytogenetics is that not all laboratories are created equally. Sometimes we really feel like a patient has high-risk disease: they have a high LDH and they have a high beta-2 microglobulin, they have normal renal function, but we get these cytogenetic results back and they say there's normal cytogenetics. And we know that that's probably not the case.

And so, in those situations, we lean on the more clinical features, the laboratory features, that can help us determine high risk. But the hope is that all patients have access to a high-quality laboratory that can give them the important cytogenetic information.

Mary DeRome (MMRF): Yes. Certainly, FISH-based testing will take you only so far; really, the gold standard is more the sequencing type of testing, right? The next-generation sequencing for some of these patients, if they can get it.

Jonathan Kaufman, MD: Right. And I think it's sort of, "The future is now." That's the future state, and we're there now. I would say for the most part, our

current guidelines are all based on FISH-based testing, and I think the future is going to be a more sophisticated testing like next-generation sequencing, as you mentioned.

Mary DeRome (MMRF): Sure. So, Steve, let's talk a little bit about your patient journey. How did you first learn that you had myeloma, when you were diagnosed? Do you recall at what point in your journey you were told that your myeloma was a high-risk subtype?

Steve Hoofnagle: Certainly. Thanks for having me. I'm excited to be here. During an annual physical in 2010, I had high protein in my urine, and my primary care physician sent me to a nephrologist who saw me for about 9 months, doing 24-hour urine collections and various things.

And then he finally said, "I'm going to send you to a hematologist," which kind of caught me by surprise. I went to the hematologist, part of a large group, and they diagnosed me with MGUS (monoclonal gammopathy of undetermined significance), which really sounds scary. But that was in 2010.

Mary DeRome (MMRF): A lot of big words there.

Steve Hoofnagle: Yes. But a doctor at that group, who was in a different hospital in Atlanta, he monitored me. I probably went in every three months for blood work, and they did bone marrow biopsies. And they also did skeletal survey x-rays. And then, in 2018 or 2019, he said, "Look, your M spike, your monoclonal protein number, is getting high. We want to try and do something." So, I did six months of chemotherapy there before they sent me to Emory.

And the first oncologist there at the other hospital there mentioned that I was high risk.

Mary DeRome (MMRF): Interesting. It was good that he was able to refer you to some great specialists there at Emory. They have a really active myeloma program, with Dr. Kaufman and his colleagues, there at Emory. So, that was a great move on your part. It is so important when you're newly diagnosed, and you really should be seen by somebody who's a specialist in multiple myeloma and sees lots of patients, because that will ensure that you're getting the most up-to-date and best standard of care when you do something like that.

Let's shift gears a little bit to the management of high-risk disease. Dr. Kaufman, how do you manage patients who have high-risk disease? Is there a standard approach to first-line treatment for high-risk patients? Or does it depend on the patient's unique risk profile?

Jonathan Kaufman, MD: Yes, great question.

We've focused for 10 to even 15 years on using a different approach for high-risk patients, because we realized that our standard approach wasn't getting the outcomes that anybody was satisfied with. And the principle that we based this on was that we found out that our induction therapies, our initial therapies, were working the same whether the patient had standard risk or high risk. And so, our approach for high-risk patients is, whatever is the best available therapy [for] induction, that's what we've been doing.

We've had a variety of therapies over the years, using lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone (RVD) or carfilzomib (Kyprolis), lenalidomide, and dexamethasone (KRD). And now, our approach as a standard is to use a four-drug treatment program using the monoclonal antibody daratumumab (Darzalex; dara) with RVD or KRD. Our approach has historically been RVD. It's very reasonable to give dara with KRD.

But that's not really where we've done most of our work, because the problem wasn't getting patients into remission, the problem was keeping patients in remission. And so, that's where we've had a postinduction strategy of strong encouragement for early high-dose therapy and transplant and then, after that, an aggressive maintenance approach. And so, going back, again, 10 or maybe even 15 years, we were reintroducing RVD after transplant, and we did it in a way that was easier on the patient, with weekly dosing of bortezomib, lower doses, rapidly tapering dexamethasone, lower doses of lenalidomide, and we planned on that three-drug therapy for up to three years followed by Revlimid maintenance.

Mary DeRome (MMRF): Wow.

Jonathan Kaufman, MD: Subsequently, we have investigated additional therapies. Based on clinical trial data from the FORTE study that came out of Italy, we switched to carfilzomib with Revlimid as part of our standard. And then, our colleague Dr. Ajay Nooka wrote a clinical trial, asking the question, "Can we use second-generation drugs?" And that was the carfilzomib, pomalidomide (Pomalyst), and dexamethasone three-drug regimen. In fact, that's the study and the treatment that Mr. Hoofnagle participated in.

Mary DeRome (MMRF): Okay. Did Dr. Nooka present some of that at the ASCO (American Society of Clinical Oncology) meeting this past year?

Jonathan Kaufman, MD: Yes.

Mary DeRome (MMRF): Yes, that was a great presentation.

Jonathan Kaufman, MD: He presented at ASCO, and the data really look fantastic. And now we're building on that, teasing out our next generation of options. That trial is finished. We do have another trial right now, using

belantamab mafodotin-blmf (Blenrep), and we know that's no longer available commercially, but it's still available in clinical trials. We have a clinical trial for high-risk patients with belantamab given every eight weeks, really spread out to decrease the risk of the eye toxicity, with pomalidomide and dexamethasone.

But the principle is optimal induction therapy, early transplant, something morethan standard and maintenance. And I think we're going to continue down that path.

Mary DeRome (MMRF): Yes, that's great. You guys are really on board with fairly aggressive maintenance therapy, I think. You sort of characterize it as that in comparison with what other centers may be doing.

Jonathan Kaufman, MD: Right.

Mary DeRome (MMRF): So, whatever works, as long as it's not too toxic on patients.

Jonathan Kaufman, MD: Right. Yes. I think that's a major part of what we do. I think Revlimid is a very good agent for maintenance therapy. I just don't think it's enough as a single agent for patients with high-risk disease.

Mary DeRome (MMRF): Agreed. And like you said, the important part is getting them into a remission phase and then keeping them there, right?

Jonathan Kaufman, MD: That's right.

Mary DeRome (MMRF): And giving a more aggressive therapy probably has a better chance of keeping them there longer, especially if they're a high-risk patient.

Jonathan Kaufman, MD: That's been our approach.

Mary DeRome (MMRF): Yes. That makes sense.

Speaking of adverse events, Sara, how do you have to approach the management of patients with high-risk disease, who may be receiving a more aggressive therapy for a drug at induction and then three drugs at maintenance? Do you see more adverse effects when you're treating high-risk patients in this more aggressive manner?

Sara DiCamillo: It's definitely quite possible, when a patient is on more drugs, that we may potentially see more adverse effects. But no, in general, I would say that our standard-risk patients and our high-risk patients both have the potential for adverse effects, and the high-risk features by themselves do not cause the adverse effects. That being said, it is true that in patients who have a higher

disease burden and start treatment, we may see more side effects or adverse effects. And some of those patients are high risk, but not all of them. So, it's definitely not a cause.

And either way, we monitor patients very often and speak a lot about those side effects and try to manage them, with the goal to have patients continue therapy and get the best response from the treatment that they can.

Mary DeRome (MMRF): Yes. That makes perfect sense. Dr. Kaufman, we talked a little bit about patients who might start off at diagnosis as being a standard-risk patient and then maybe progress to being a higher-risk patient later in their disease. How is their treatment managed differently once that transition occurs to a higher-risk state?

Jonathan Kaufman, MD: Sara mentioned this concept of functional high risk. We consider patients who have progression within two to two and a half years of diagnosis to be considered functionally high risk. One of the things we have, as you know, is the MyDRUG study that's available for those patients.

That study looks at these functionally high-risk patients and asks the question, "Is there some sort of specific molecular abnormality that we didn't identify on the FISH testing that would have clued us in that you're high risk, and can we target those?" So, that's one option.

But if we identify a patient as high-risk, it's not necessarily true that I would choose a different drug, but there might be some management decisions that I would do differently. For example, patients who have standard-risk disease can often have evidence of progression, the return of the monoclonal protein, and we'll often observe that and keep an eye on that. And the time from recurrence of the protein until somebody needs treatment can often be six months, nine months, a year, or more.

With high-risk patients, people who have high-risk features, I'm much less likely to observe, because I think that period of observation is likely to be very short and could be associated with symptoms. And so, it's not necessarily the treatment that is different, but more so the treatment strategy, really trying to stay on top. More than anything, patients with high-risk disease really need those deep remissions to stay in remission for a long time.

Mary DeRome (MMRF): So, is MRD (minimal residual disease) testing part of the way that you follow these patients, especially at certain time points in their therapy?

Jonathan Kaufman, MD: Yes. Certainly, in newly diagnosed patients who are planning for a transplant, we check MRD before transplant, after transplant, and then yearly from there.

Mary DeRome (MMRF): Yearly. Okay.

Sara, we talked a little bit about transplant and how early transplant is a big part of standard of care, especially for patients with high-risk disease. That is part of what you guys do at Emory, right, encourage people, even high-risk patients— especially high-risk patients— to undergo an early transplant?

Sara DiCamillo: Yes. Exactly. As you know, and as Dr. Kaufman mentioned, that is the standard of care for us here at Emory. There are a lot of different opinions around the world about transplant in standard-risk versus high-risk patients, but I think with the data that we have now, most people would agree that, particularly in the high-risk population, we will proceed with a transplant.

Mary DeRome (MMRF): Yes. Steve, let's talk about your situation. You had a transplant about four years ago. Tell us how that went.

Steve Hoofnagle: It was four years and seven days that I got out.

Mary DeRome (MMRF): Not that you're counting.

Sara DiCamillo: Congrats.

Steve Hoofnagle: Facebook memories.

Yeah. On August 19th I went, of 2019, following six months of chemotherapy at the other hospital. There were about six weeks, maybe four or five weeks, of pretest clearances and so forth, and I had to get a Trifusion central line put in and so forth. I was in a little bit longer because, unfortunately, I got a little bit of *C. diff (Clostridioides difficile)* while I was in there. But the procedure found everything, all the hemapheresis for the collection and all. You just had to go in there, and the people took great care of you. So, it was 17 days that I was in there, and then I was on home recovery for about 5 weeks after that and would come in for labs. But overall, as scary as it might sound, it's really not. You just take it one day at a time, and these people are professionals, and they know what they're doing.

Mary DeRome (MMRF): Okay. Dr. Kaufman, we talked a little bit about maintenance treatment in the high-risk setting and the fact that you guys really take a much more aggressive approach to maintenance with patients who are high risk. I know that we talked about your using dara along with a three-drug regimen for induction, but is there dara involved in the maintenance of high-risk patients, as well?

Jonathan Kaufman, MD: A very timely question. I would just say, historically, we haven't. We have gone with the combination of a proteosome inhibitor (that's the Velcade or Kyprolis) with an immunomodulatory drug (Revlimid or Pomalyst).

And in looking at our data, we still see certain subsets of patients not doing as well as we'd like. So, we're currently talking about designing strategies to reintroduce daratumumab back into the maintenance approach and seeing if we can turn that subset around that's still not getting as much benefit as we'd like out of these treatments.

Mary DeRome (MMRF): Yes. That makes sense. That would probably be putting these patients into more of a clinical trial setting, if you were going to put them on Darzalex along with a number of other therapies in the maintenance setting.

Jonathan Kaufman, MD: We have other clinical trials. We don't have a clinical trial for that approach right now. That would be a practice pattern, as opposed to a specific clinical trial.

Mary DeRome (MMRF): Got it. So, then, what are some of the really interesting trials that you have ongoing for high-risk patients?

Jonathan Kaufman, MD: The trial that I mentioned before, for maintenance therapy, uses the belantamab mafodotin with pomalidomide and dexamethasone. We had a recent trial that I think is a great idea and I think should be explored further, for patients who fail to achieve a major response after transplant, this concept of functional high risk, to do early chimeric antigen receptor (CAR) T-cell therapy for those patients. I think that's a great idea. We don't have a trial open like this, but the concept of early CAR T-cell therapy or early bispecific antibody therapy is something that we're very interested in.

In fact, we had a meeting this morning where we're designing a whole comprehensive trial of introducing all of these new therapies earlier. Our approach is to do this for both high-risk and standard-risk patients, and we think that the high-risk patients might really benefit from moving these drugs that we currently use very late to much earlier in the course.

Mary DeRome (MMRF): Right. I was just going back through my slides that I had taken pictures of at ASCO, and that's where they had that amazing presentation about the CARTITUDE-4 trial using CAR T-cell therapy very early, after second relapse or something like that. Right?

Jonathan Kaufman, MD: Right.

Mary DeRome (MMRF): Those data were just so amazing. It was so shocking that it was so effective.

Jonathan Kaufman, MD: Right. Right.

Mary DeRome (MMRF): And I'm sure that we'll be seeing more of that as the pharmaceutical companies are now trying to get these CAR T-cell therapies approved for this newer indication, in earlier lines. Right?

Jonathan Kaufman, MD: Right. Exactly.

Mary DeRome (MMRF): So, we might even see one of those approvals this year; if not, early next year.

Jonathan Kaufman, MD: I'm not in the know.

Mary DeRome (MMRF): Neither am I. All I can say is what I've heard.

Steve, you were in the clinical trial to treat your high-risk myeloma. Can you tell us a little about that? What was your treatment, and how long were you in that trial?

Steve Hoofnagle: Certainly. As Dr. Kaufman mentioned, I was in the trial that used the Pomalyst, Kyprolis and dexamethasone. I did 36 cycles, 28 days per cycle. I would go in three times, on Thursdays, and I would have the infusions. And then I got seven days off for recovery. That started back on November 25th of 2019 and wrapped up this past October. Probably the biggest thing that I didn't enjoy was the dexamethasone.

And I don't think any of my friends and family did either. I was getting big doses in the beginning, and they would call them “roid rage Thursdays.” So, they reduced that for me.

Mary DeRome (MMRF): I don't think anybody likes that drug. Really, it's terrible. So many people complain about it. It's awful. Although, finally I have seen some clinical trial data where they've been trying to either really, really reduce the dosage of dexamethasone or eliminate it entirely, especially for those people who are older and more frail because those are the people that I think really have the adverse events having to do with dexamethasone. We'll see what happens with that. It is a good drug, and it certainly is helpful in myeloma. But if it can be managed better, I think everybody would be much happier. And families would also be much happier.

Steve Hoofnagle: Caregivers too. They had to put up with me for 36 months.

Mary DeRome (MMRF): That's what I'm saying. Right. It can be hard.

Dr. Kaufman, I think we talked already about the newer myeloma treatments like CAR T-cell therapy and bispecifics.

Can you give us a summary of how effective these types of treatments are for patients who have high-risk disease versus some of the other standard-of-care therapies?

Jonathan Kaufman, MD: The newer therapies, bispecifics and CAR T cells, are also effective in patients with high-risk disease. I think that, similar to what we've seen with all of myeloma, there is probably a little lower overall response, but it's still much better than anything else that's out there. Always, the concern is for the shorter duration of response.

Having said that, the key features that we've seen associated with, I would say, lack of benefit is the burden of disease. Certainly, burden of disease is associated with more side effects at the time of bispecific therapy and CAR T-cell therapy.

And so, one of the things that we've started moving towards—because right now they're all fourth line—is not waiting for the patient to have fourth-line therapy and a maximal amount of disease, but really trying to identify who is high risk very early and trying to treat with these newer therapies when the patient has a lower disease level, which I think is probably more important, especially from a toxicity perspective, than the specific cytogenetic abnormalities.

In a large part, once a patient has had four or five lines of therapy, there's a smaller difference between somebody who has a cytogenetic abnormality and somebody who does not have a cytogenetic abnormality.

Mary DeRome (MMRF): And there's also the issue of sequencing these therapies, which is an area of very active investigation right now. And also, combinations with some of these therapies, even combinations with CAR T cells. We saw some really interesting data at ASCO combining two different bispecific antibodies with different targets, which was quite interesting, the TRiMM-2 study.

Sara, what sort of ongoing monitoring is done for patients with high-risk disease? Is that really different compared with what you might do for monitoring for patients who have standard risk?

Sara DiCamillo: I would say largely this looks very similar, Mary.

For most patients, as Mr. Hoofnagle mentioned, they come in monthly. They have labs. We go over their chemistries, their blood counts, how they're feeling, anything that's changed. And this is really the part of my job that I love. We get to know patients and their families well. We get to know what's normal for them and what’s not normal, so we can monitor anything that's new or concerning.

In addition—and Dr. Kaufman talked about this—we do bone marrow biopsies yearly with an MRD test. In patients who have extramedullary disease, this would

be a little different: They would have more regular scans, just because of how their disease presents. But I would say largely it's similar. There might be a few differences in follow-up as well. We might let a patient who has standard risk, who is in a complete remission, go a little bit longer between labs and visits, and, just because we know the history of how high-risk disease presents, we make sure we see those patients routinely.

Mary DeRome (MMRF): Do you have frequent conversations with your patients about how their therapies are going, whether or not they might want to back off on some things or potentially take a drug holiday? We had a couple of recent programs where we talked to patients who have been adamant about that with their care teams. Once they get into a remission phase, many of them just want to stop treatment for a period of time (while being closely monitored, obviously) until they begin to have a biochemical relapse or something, which is probably not what you would recommend to a patient who has high-risk disease, right?

Sara DiCamillo: Yes. In general, I would agree. We don't really recommend stopping treatment for a long period of time. Of course, if a patient wants to travel or be gone and miss a treatment here or there, that's fine, but we wouldn't recommend just stopping treatment entirely. A lot of patients ask that question: if they're in a remission, can they just stop?

And as we know, because the disease can come back, and come back aggressively, obviously that's not our goal. So, we do encourage staying on treatment.

And to answer the first part of your question, yes. I tell patients the purpose of that monthly visit and seeing patients often is we want to know that the medication is working and that patients are tolerating it. I don't think we're doing our job well unless we're doing both. I have some patients who are reluctant to tell me how they're feeling, and they think they're complaining, and I remind them, "You're not complaining. This is what we're here for."

Mary DeRome (MMRF): Yes. Right.

Jonathan Kaufman, MD: We want to hear how patients are doing, and we can dose-adjust medicines, as you mentioned, if needed, or decrease dexamethasone as needed. And so, yes, a big part of that monthly monitoring and knowing patients well is being able to adjust medicines, and the goal is to allow these patients to live their lives fully while still being on treatment that hopefully keeps them in a remission.

Mary DeRome (MMRF): Right.

That level of communication between the care team and the patient is so vitally important. If the patient is experiencing a side effect and they don't tell the care

team about it, then the care team can't help with whatever is happening with them. It's really vitally important. And like you mentioned, it's not complaining. It's just saying, "Okay, I'm taking this drug, and here are the things that I'm feeling. Can you help me? Because it's really impacting my quality of life." That's an important point.

Steve, we already talked about the fact that you're in the maintenance therapy phase of your treatment. Can you tell us a little about what's happening with you, what ongoing monitoring you're having, the testing that you do? And how does that impact your quality of life? And do you find that scheduling of the dosing and then the testing is manageable for you?

Steve Hoofnagle: Yes. Anybody that lives in the Atlanta area knows it takes an hour to get to Atlanta from Atlanta, anywhere.

Mary DeRome (MMRF): That's the truth. The traffic there is terrible.

Steve Hoofnagle: That was a big part of it. And we've actually relaxed me to only coming in every two months now.

Mary DeRome (MMRF): Oh, wow.

Steve Hoofnagle: I do the bloodwork and also get hep-lock in my port. I still have my port. But I'm on a 2 mg dose of Pomalyst, 21 days on, 7 days off. I come in for bloodwork. On my next visit in October, we're doing my annual bone marrow biopsy and MRD testing. During the clinical trial, we did a lot of other things, echocardiograms and skeletal surveys, that we're not going to do on a routine basis now. But it's very manageable for me. It's been a good experience. I'm very grateful for the health care professionals there at Emory.

Mary DeRome (MMRF): Yes. So, you're in a good spot. That's for sure.

Let's move on now to some final thoughts. I've got some final questions for everyone. Steve, we're going to start with you. We're going to talk a little about side effects. You already mentioned that you were having some issues with dexamethasone. Were there any other side effects that you had from any of the other medications that you were taking? And how did you manage that?

Steve Hoofnagle: No, I really didn't seem to feel any. There were other patients who were in the infusion areas that had to be treated for nausea and things like that. I didn't really have any of those problems. And my kidney function has been outstanding. We're still doing a quarterly urine collection for me because I still see the nephrologist and he likes that information.

Mary DeRome (MMRF): Well, I guess that's a good outcome, considering that you're a high-risk patient, that you're taking this fairly aggressive treatment and you're managing to have a decent quality of life with that, which is great.

As long as you don't have to drive from Atlanta to Atlanta for an hour.

Steve Hoofnagle: Yes, ma'am.

Mary DeRome (MMRF): Sara, how do a patient's comorbidities, other medical conditions that they may have alongside their myeloma, factor into their management when it comes to high-risk disease? For example, how would you treat a high-risk patient with severe kidney disease?

Sara DiCamillo: It's a good question. We think a lot about which medicines we're using and how they're metabolized and cleared. For an example, in induction therapy, Dr. Kaufman mentioned that we usually use daratumumab in combination with Revlimid, Velcade, and dexamethasone. In a patient who presents with severe kidney dysfunction, we would not want to use the Revlimid. We would start the patient on daratumumab, Velcade, and dexamethasone (dar-Vel-dex), or we could use thalidomide, which is in the same drug class but which we don't have to renally dose (dose adjustments made for patients with kidney disease). So, it's much safer for those patients, and patients still have a great response. And then, if, hopefully, the kidney function improves and stabilizes, we can transition these patients to Revlimid.

There are other drugs, too. Talking about Kyprolis, it can cause heart toxicity, so, in a patient who might have some underlying cardiac issues, we might try to use a different drug or monitor them more closely and things like that. We're always thinking about those underlying comorbidities and how to monitor closely to make sure that we're not harming the patient.

Mary DeRome (MMRF): Yes. It can be kind of complicated. Because these patients are taking so many drugs at the same time. Plus, they may have some other, unrelated, conditions that they're taking drugs for as well. So, there's always a chance for these things to interact with each other.

One final question for you, Dr. Kaufman. What are the goals of treatment for a patient with high-risk disease? And is MRD negativity achievable for these patients?

Jonathan Kaufman, MD: The short-term goal for a high-risk patient, as well as for standard-risk patients, particularly if they're symptomatic, is to decrease the tumor burden, the myeloma burden, enough to get rid of the symptoms: bone pain, kidney dysfunction, anemia, fatigue, and those types of things. And often, a patient who feels very bad, even though we're giving them drugs that have a laundry list of potential side effects, a month later, they feel better. Now, a lot of

patients don't necessarily feel bad, if they're diagnosed because their numbers are rising, and so our goals are to really get a deep remission and have that deep remission last as long as possible.

So, our goal is to find the therapy that has the highest chance of achieving MRD negativity.

We don't know if we're going to get there, but we want to give the patients, especially high-risk patients, the highest chance of that MRD negativity. And that's why we recommend all of those aggressive therapies back to back to back, because achieving MRD negativity with this treatment is associated with staying in remission longer. And absolutely, high-risk patients can have MRD negativity and can stay in remission for a long time. We're seeing a patient right here who's in that boat.

Mary DeRome (MMRF): Yes. I think we're still dealing with about, what, 20% to 25% of patients who are in that high-risk–disease boat, right?

Jonathan Kaufman, MD: Right.

Mary DeRome (MMRF): And for a long time there just wasn't any way to treat these patients in a way that really prolonged their life; the standard-risk patients were achieving better survival. But now there's so much research and clinical trials really focused on this issue, that I think patients who may be diagnosed as being high-risk patients when they're newly diagnosed have a lot of things to look forward to. And survival is really increasing for these patients, based on some of these newer drugs and newer combinations of drugs. I think that will only get better for these patients as time goes on, which is really a great thing, because they are the ones who have the most unmet need.

Jonathan Kaufman, MD: Right. And I think you mentioned the key is that we have clinical trials specifically designed for high-risk patients. Historically, we gave the same thing to everybody, and then the high-risk patients didn't do as well, and then we said, "Well, the high-risk patients don't do well with this treatment."

We moved away from that. We're doing this at our center, we're doing this within cooperative groups, the French are doing this: designing specific clinical trials for high-risk patients, asking specific questions, and then advancing the field from there.

Mary DeRome (MMRF): Yes. From the data that I've seen at some of these meetings, we are having some success in treating patients who have certain chromosomal abnormalities, although the 1q amplification continues to be one of the tougher ones to treat, right?

Jonathan Kaufman, MD: Yes.

Mary DeRome (MMRF): So, they still need to do some work there.