FAQs on Newly Diagnosed Multiple Myeloma

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Transcript

Mary DeRome (MMRF): Hello, everyone. Welcome and thank you for joining us for today's session on frequently asked questions on newly diagnosed multiple myeloma. My name is Mary DeRome. I'm senior director of medical communications and education at the Multiple Myeloma Research Foundation.

Today, I am joined by Dr. Gurbakhash Kaur, and Miss Sonia Patel from the UT Southwestern Medical Center in Dallas, Texas, and Don O'Connor, who is one of their patients from Fort Worth Texas.

We have a number of questions from patients and caregivers about initial treatment, maintenance therapy, and monitoring for newly diagnosed multiple myeloma.

Dr. Kaur, for a patient who's just been diagnosed, how do you and the patient decide on the best course of treatment? For example, do specific test results like the presence of cytogenetic abnormalities influence the choice of a particular regimen?

Gurbakhash Kaur, MD: Thank you, Mary. Yes, so there are several initial tests that have an implication on how we end up selecting the regimen. Prior comorbidities, and the existence of neuropathy does play a role, but most importantly, it's the cytogenetics. Anybody who has high-risk cytogenetics; that is the t(4;14) deletion, 17p, or TP53, even amplification 1q, we tend to use quadruplets such as Darzalex-Velcade-Revlimid-dexamethasone (DVR-d) versus a triplet. Also, we use beta-2 microglobulin, albumin, and lactate dehydrogenase (LDH) test results, along with the cytogenetics to stage the patient.

The higher RISS 3 and 2, particularly, we use a quadruplet. Although I think more and more, the myeloma community has moved towards a quadruplet in general. For the most part, that's what guides us.

Mary DeRome (MMRF): Yes, I think that's what we've heard, too, and I was going to ask you that question, but I'm glad you clarified, because I do think that the more you talk to people, the more it seems like quadruplets are becoming the new standard of care upfront, whether or not you have high-risk cytogenetics. I've heard that from a number of folks.

Gurbakhash Kaur, MD: Yes.

Mary DeRome (MMRF): So, Sonia, what about patients who have a precursor condition like monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma? Those patients just want to know why they don't require treatment, and many comment it's just really hard to sit and wait. If you have a patient who has one of those conditions, how do you counsel them about their course, what they're going to be facing for the next few months?

Sonia Patel, MPH, MSN, APRN, AGACNP-BC, AOCNP: Thank you for having me today. I'm thrilled to be here. To answer your question, currently, there's no data to support that treating these underlying conditions will actually cure their disease or necessarily delay progression to multiple myeloma. Luckily, many patients remain asymptomatic with these conditions. It's also important to note that not every MGUS patient will necessarily progress to multiple myeloma, and if and when they do, it can often take several decades. Although it is difficult to sit and wait, like you say, we want to avoid any unnecessary treatments for as long as a period is possible, just given the potential side effects.

When someone does start on treatment, it becomes a lifelong commitment to ensure the disease stays well controlled, and we want to avoid interruptions in treatment in the future. I often counsel patients and let them know that we will be monitoring these precursor diseases closely, with routine labs, imaging, bone marrow biopsies, and visits at specified intervals. It often helps to review their specific disease criteria and their assigned risk based on this, to help reassure them further.

Mary DeRome (MMRF): Can you talk just a little bit about the frequency of visits of an MGUS patient versus a smoldering patient?

Sonia Patel, MPH, MSN, APRN, AGACNP-BC, AOCNP: Certainly. When we first meet either, we have specific lab values and data that we want to monitor, and those assign them to a specific kind of risk category. Typically, with our MGUS patients, we feel comfortable monitoring them every three to six months, that first year of meeting them. If that's stable, then we can go to annual lab visits with them. For smoldering multiple myeloma, we are wanting to monitor them more frequently, maybe every three to four months, and will be monitoring these values closely.

Mary DeRome (MMRF): Great. Thank you for answering that question, because that's a question that we get fairly frequently.

Gurbakhash Kaur, MD: Mary, I just want to add one thing to this, Sonia is very right, with smoldering myeloma, we do watch and keep a close eye early on, to see the rate of rise in their parameters. And if it's stable, we can even go to six months for certain patients who have low risk. There's a whole set of 20-2-20 criteria that we use to assess risk status. And while there is some debate in the myeloma community, right now, whether to treat high-risk myeloma, and

certainly, there is one trial that does support the use of lenalidomide, there are several ongoing trials. So, at the present, Sonia and I do not treat MGUS or smoldering myeloma at all with medications. High-risk myeloma is the only one where we will treat in the setting of a clinical trial. But outside of that, we observe.

Mary DeRome (MMRF): Yes, great. Let's go to our patient, Don. So glad you could be with us today, Don. Can you tell us how you were diagnosed with myeloma, and how were you able to connect up with this amazing treatment team at UT Southwestern?

Don O'Connor: I do have a great team, that's for sure.

The way that I was diagnosed was, I was on vacation and tried to lift a suitcase into a taxi cab, but my back hurt so bad I couldn't even lift up a suitcase. I went to my primary care doctor to try to figure out what's going on. That led to a spine clinic where I got some steroid shots.

Mary DeRome (MMRF): The usual, right?

Don O'Connor: Yes, they didn't work. Then luckily, though, the senior surgeon at that spine clinic, after the first set of shots that didn't work, he contacted me and he said, "I think we need to check you for cancer." And it was just like that. I was looking at backache, and all of a sudden, he says "check you for cancer." So, that was startling, and I talked to everybody that I could, if I walked down the hall at work or at the condo, I would ask, if I thought those people were in the medical business, "What should I do? What should I do?"

And the advice was: finding a hospital that has a specialty for multiple myeloma. It was, "Don't go down to your local general oncologist in a small town. Find a specialist." So, I'm in Fort Worth, I start to do my research, and it gave me three choices. I ended up with three choices: MD Anderson, UT Southwestern, or Mayo Clinic. And two of them were going to require a lot of travel. But I first contacted UT Southwestern, trying to get in touch with Dr. Anderson, and he said he could see me in four months. Well, at this time, I had seven broken vertebrae. Two months prior, I only had two broken vertebrae. I'm thinking by four months I'll have – everything will be broken. I can't wait.

I followed through with the contact for Dr. Hayman at the Mayo Clinic and we were set to do that, but the next day, I got the call back from Dr. Kaur to come here and she'll treat us right away. And I say, us because my wife is pretty much here every step of the way, except for right now she's not here with me. She's gone to get my medicine at Walgreens.

Mary DeRome (MMRF): Oh, there you go, so she trusts you to talk to us.

Don O'Connor: Yes. So, after all of that, we met, came up with a plan, and I was hooked. I needed to do something quick, because I thought, in my mind, that it was going to get bad really fast.

Mary DeRome (MMRF): Yes. How long did it take between the time that the doctor said you need to be checked for cancer and then you were actually diagnosed with myeloma?

Don O'Connor: I couldn't leave the house. I was, by this time, I was in a wheelchair. As soon as she said that, my primary care doctor came to the house, did bloodwork and sent it off. That was the week before Easter, last year, so that would've been middle of April. So then by the following week, they said, "All the bloodwork's come back. We can't prove that it's cancer, but the bloodwork says we can't disprove it, either. So, we think you need to make the next step." Which then, by May, I was there; I was able to get in to see the doctor. And Dr. Kaur said, "The tests aren't in, but I know what I'm doing and this is multiple myeloma." And she was right.

Mary DeRome (MMRF): I bet that made you feel much better, right?

Don O'Connor: Oh, yes, I had a very confident and capable doctor, so, I'm happy.

Mary DeRome (MMRF): Good, good for you.

Don O'Connor: It was maybe total six weeks at the most.

Mary DeRome (MMRF): Okay, and that's not so bad. Dr. Kaur, with Don's history, having vertebral fractures like that is actually not a rare occurrence for myeloma patients. Out of the patients that you see at newly diagnosed stage, how many of them actually present with that as their first sign?

Gurbakhash Kaur, MD: You know, myeloma is just not one disease, I would like to say, it's multiple diseases. Recently many people have been commenting on that, because while many of my patients do come with fractures, whether it's rib fractures, vertebral fractures, hip fractures, there are some who don't actually have a single bony lesion. So, there is a heterogenous presentation, but I would say more than 50%, 50 to 60% of patients end up having some kind of bony involvement.

Mary DeRome (MMRF): So, knowing, Don's history and his case, when you have these bone lesions and you have treatment of induction therapy, does that help the pain? Do the bone lesions heal completely, after you begin the therapy? Or do you have to give other treatments, as well?

Gurbakhash Kaur, MD: Along with induction therapy, whatever it may be, you have to control the disease with antimyeloma therapy, with the monoclonal antibody or a proteasome inhibitor like Velcade and IMiD, along with dexamethasone. You have to control the pain; symptom control is at the mainstay of treatment. You have to control the disease, and there is healing, although not completely all the time. Sometimes, I do palliative radiation, if I just know that the pain is unbearable.

We have to get fast control and the treatment's not going to kick in right away, pending patient symptoms. And we also do antiresorptive therapy with either Zometa or Xgeva. Usually, I like to do that for two years post, once a patient is diagnosed. The treatment of vertebral fractures or just bony disease is multifactorial.

Mary DeRome (MMRF): Sonia, aside from bone fractures and pain, what other symptoms that are caused by the myeloma do patients frequently experience? And then, similar to with the bone lesions, once you start treatment, do the symptoms actually go away?

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: Some common other symptoms that patients may present with initially include fatigue, weight loss, sometimes lower immunity, and neuropathy. A lot of the time, patients are presenting with symptoms associated with anemia, that's extreme fatigue, shortness of breath when they're exerting themselves.

The symptoms can improve after treatment's initiated, given that the anemia often resolves. However, just by nature of the chemotherapy agents that we use, fatigue can be a side effect. So, it doesn't always go away completely. In particular, as we mentioned, we use steroids as part of our regimen, dexamethasone. Usually in people who are 70 years or younger, we'll give them 40 milligrams weekly. If they're 70 years and older, this can be reduced to 20 milligrams weekly. Some people can often have what's called a dexamethasone withdrawal, where they go from being very awake, alert for an extended period of time, and then kind of sort of crash and become very fatigued and low-energy.

It's important to check in with our patients frequently, to see how they're tolerating the dex and address their concerns of insomnia, fatigue, and see if any dose adjustments are warranted. You also have to be careful with monitoring their blood glucose levels. The steroids can raise this in certain individuals or make underlying diabetes worse. We have a great team of endocrinologists that we use to help treat blood glucose, if we feel like they're trending upwards.

Also, Revlimid, an oral chemo agent that we use, a lot of people will have fatigue with that, some diarrhea, constipation, at times rash. We're constantly managing these symptoms supportively, as they arise.

Mary DeRome (MMRF): Sure, so it's really just a lot, right? There's a lot going on, there.

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: Yes, a lot.

Mary DeRome (MMRF): Don, once you were diagnosed, what was the initial treatment that you received, and how did you decide on that treatment? Did you get a second opinion when you were trying to make your decision?

Don O'Connor: After diagnosis, Dr. Kaur thought that I would fit well into a trial. I don't know all the right jargon, triplets, quads, whatever, but from my trial, I was doing dexamethasone, Revlimid, and the antibody, Darzalex. Those were my three medicines, and once we got in a couple of months, we started to add in the bone medicine, Zometa, to try to keep things going. Dr. Kaur told me that was going to be the plan and that was how it was laid out.

It just so happened that I had a video meeting scheduled with Mayo Clinic to decide if I was going there or staying in UT Southwestern. I explained the test and the trial to her and she said, "Sounds great,"

Mary DeRome (MMRF): Oh, there you go.

Don O'Connor: That was my biggest surprise of the whole process, I think. She said, "I really like what you're getting into. I wouldn't come here if I was you." That's what she told me. She said, "You'll be much more comfortable at home, you're welcome to still come here," and I thought, "Wow, that's a great plan, and if she agrees with it and UT Southwestern agrees with it, then that's the one to go through."

Mary DeRome (MMRF): Dr. Kaur, many patients believe that a clinical study is only for patients who have run out of options, but clearly, you put Don on a clinical trial for his first therapy, which is pretty amazing as his initial treatment. Should all patients be asking their care teams about clinical trials, right after diagnosis? Is it appropriate for all patients?

Gurbakhash Kaur, MD: Yes, I think you should always be asking your providers or your doctors and your team about what are all the options. You want to get the best opinion and the most open opinion, granted that the therapy has to be tailored to the individual. I think that's often a misconception, that trials are often the last resort, and there might be a placebo.

Sonia and I spend a great deal of effort in our first meeting, because that is where we lay the foundation of our relationship with the patient. Trust is an important aspect of that and competency, those two factors. I think we established that with Don very well, when I said, "Come here. We're going to

figure this out. We're going to treat this, I'm not going to delay your treatment, because you need it." Because, like he said, "I would've gone to any place."

There was a sense of urgency which I noted given what was going on with him. I think when it's newly diagnosed the stakes are obviously higher; the clinical trial has to be well-thought-out, as well. Darzalex, the trial that we have, is an minimal residual disease (MRD) risk-adapted trial. Darzalex has been in treatment for almost – close to a decade now. Revlimid has been around for 15, 20 years, and dexamethasone, and along with Velcade.

These are proven therapies; we're sequencing them to understand who are the patients we're overtreating and undertreating. Don is young and there weren't any high-risk features on his bone marrow, his staging was stage one, RISS I, so we felt very comfortable having that discussion. Even outside of the trial, he would've gotten either DVRd or VRd, depending on what we chose. I think because we have that foundation and that trust, Don came onboard. It didn't take a lot of convincing to actually do that, right, Don?

Don O'Connor: Correct. It didn't take long to trust in the care team.

Mary DeRome (MMRF): Oh, that's good.

Gurbakhash Kaur, MD: Yes.

Mary DeRome (MMRF): Other patients appreciate your efforts, Don, because this is how new therapies get approved all the time. Patients have to go on trials and that's how these things become standards of care.

Sonia, many newly diagnosed patients who may be watching are about to start their induction therapy regimen, so, let's talk a little bit about what patients can expect. This is a broad question, and your answer might be different depending on the regimen that any patient will be receiving, so I'm going to ask you a series of questions. In general, how often will a patient have to come to the hospital or clinic to get treated?

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: Sure. We've mentioned that induction therapy can often include either four drugs or three-drug regimens, and we're usually completing about four to six cycles in total, before making a decision to go onto stem cell transplant, or, if ineligible, some kind of maintenance therapy. Each cycle consists of four weeks in total. Many regimens use an oral drug, like we've mentioned Revlimid, you take that 21 days out of the cycle.

There is weekly dosing of some drugs that are usually administered subcutaneously, so an injection. A common one that we've talked about is daratumumab (Darzalex). It's given weekly for the first two cycles, then every-

other-week with cycles three through six, and then given monthly with cycle seven onwards.

Another one, Velcade, is also given subcutaneously. That's given weekly, four of four weeks, for the first two cycles, and then it can decrease to three out of four weeks, starting with cycle three onwards. The patient can be expected to come in quite regularly, in the beginning, for induction therapy. They're also expected to come in and see a provider at the start of each cycle, to check and assess how they're doing, and also how they're responding to therapy by monitoring their markers.

Mary DeRome (MMRF): You mentioned a couple of subcutaneous administrations, so Velcade, and Darzalex is subcutaneous, right? It's such a great advance instead of having to do anything IV. When you're doing IV administration of any medicine, it can take a long time.

Before Darzalex became subcutaneous, how long did the treatment with Darzalex take when you had to have it infused IV?

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: I think it was several hours. Wasn't it upwards of six hours? It was a very long timeframe. So, yes, it's dramatically decreased the amount of time.

Mary DeRome (MMRF): Now it's five minutes or something.

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: Yes, exactly, yes.

Mary DeRome (MMRF): Much better, much better. When you're getting an IV treatment, if you're on Sarclisa, which doesn't really have a subcutaneous administration yet, is that something that patients need to have a central port, to be able to take?

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: No, we rarely, if ever, arrange for a central port.

Mary DeRome (MMRF): It goes into your hand or whatever, right?

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: Yes.

Mary DeRome (MMRF): If you're getting a subcutaneous infusion or an IV infusion, do you need to have someone with you at your appointment to make sure that you can get home? You wouldn't give people these medicines then expect them to drive home?

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: Correct, I feel like caregivers are really essential, especially for that initial consultation, we're giving

a lot of education about the disease, how we monitor it, how I manage it, so it's a lot to absorb. It's helpful to have that person there taking notes and taking that all in.

And then, for the first few infusions, it can be a little bit longer in length, because we're delivering chemo drugs that may warrant monitoring for allergic reactions or unwanted side effects. It's helpful not only to have company for those longer days, but also to have someone present in the event the patient needs assistance getting home. If they have fatigue, nausea, vomiting, headache, fever, or anything like that.

I think with time, however, the infusions should reduce in time and sometimes frequency, like we mentioned, and a patient becomes better at tolerating the treatment and acquainted with the process, making a caregiver not as necessary for each visit down the line.

Mary DeRome (MMRF): Okay. Let's talk a little bit about autologous stem cell transplantation, because this is a very common standard of care therapy for newly diagnosed patients. We know that, following induction therapy, the typical next step is treatment with an autologous stem cell transplant, if you're eligible.

Dr. Kaur, what is the purpose of a transplant, especially if a patient achieves a deep response with their induction therapy?

Gurbakhash Kaur, MD: I think stem cell transplant still has an important role in myeloma therapy, compared to all the newer therapies that are coming onboard, it's going to be very cheap and effective. The point of a stem cell transplant is to get you a deeper response, and we know deeper responses translate into longer duration of a response. While we know, from the DETERMINATION data, that there is no overall survival benefit when you do upfront versus delayed transplant, there is a 20-month PFS benefit if you do upfront.

Now, when we decide on how someone becomes eligible, we take into consideration several factors: their age, their other medical conditions, their preference. Someone who is 50 or 60 years old, they can possibly delay transplant, because they will still be eligible by age of 65.

To finalize, the purpose of the transplant is to have a deeper response. And to achieve MRD-negativity.

Mary DeRome (MMRF): Great. Okay, Sonia, can you walk us through how patients should prepare for a transplant? Also what their caregivers need to prepare for before and after the transplant.

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: Sure. In the beginning, patients should be prepared to have many, many appointments, as they undergo

the eligibility workup for a transplant, to ensure they meet the criteria. They'll have an echo of their heart. They'll have a function test that assesses their lung health. They'll have a bone marrow biopsy, urine studies, bloodwork, and they'll also have frequent visits with our transplant coordinators, social worker, dietician, insurance coordinator, just making sure everything is lining up.

Once this workup is complete, then they have the opportunity to meet with Dr. Kaur, or their doctor, and the transplant coordinator, to review all the workup and make sure everything is in line. This is also a great opportunity for the patient and the caregiver to ask any of their questions, and go over the results and overall plan.

They then prepare for this stem cell collection where they'll get four days' worth of injections that help stimulate their bone marrow to produce more of the stem cells. They then come to our infusion wing at the clinic and undergo the collection. It takes, on average, between two and three days, and it goes through sort of a blood filtration system. Once it's completed, the product is preserved by our blood center care team, and it's stored until reinfusion happens at the hospital. After the stem cell collection is complete, the patient and caregiver, they'll have to prepare for the hospitalization.

On their first day of admission, that's when the patient will receive a high-dose chemotherapy that drives their disease in a deeper remission that standard-dose therapy alone can't accomplish. And then their stem cells are reinfused following this. The patient can be expected to stay in the hospital roughly two weeks, at most three weeks, to allow for their bone marrow recovery, with close monitoring and managing their symptoms. Making sure infection is well-controlled or whatnot.

I'd have to say the caregiver is a very, very important role during transplant. We encourage caregivers to help the patient with all their needs, and especially transportation, coming to the educational visits, learning the process as a whole.

We do require a caregiver for the first 30 days post-transplant, but half this time, as we mentioned, they're in the hospital. Once they're discharged, they're coming to us weekly for visits, for monitoring. Also, the caregiver is helping them eat, drink, monitoring for infection, staying active. They're their biggest advocate.

They let us know if anything is coming up, and they help with managing medications, groceries, preparing food, cleaning the house, as the patient is recovering during this acute time period.

Mary DeRome (MMRF): Great. This is a really interesting question that I had never received before, from a patient, on one of our webinars. The patient wanted to know if there was any incidence of administrative errors during stem cell apheresis, storage, and administration. How often are stem cells, after

collected, lost, expired, or given to somebody else, or any other kind of procedural error? Does that happen?

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: Not to my knowledge, no.

Mary DeRome (MMRF): I would imagine that people are really, really, really careful about what happens with these cells.

Sonia Pate MPH, MSN, APRN, AGACNP-BC, AOCNP: One hundred percent.

Mary DeRome (MMRF): They check and then they check and then they recheck, to make sure that everything is where it's supposed to be, and everything's labeled, and the right person is getting the right bag of cells.

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: Yes, 100 percent.

Mary DeRome (MMRF): Okay, that's what I thought, too. But people have to ask these questions.

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: Yes.

Gurbakhash Kaur, MD: It's a very valid question.

Mary DeRome (MMRF): Yes, these things happen. It's not that it has never happened, but it's extremely rare.

Gurbakhash Kaur, MD: Yes, but there are lots of checks and balances, and that's why even when the patient's cells are infusing in the room, there is the presence of nurses, the blood care team, at our center. Every center probably has a different process, and there's double-checking of the bags, verifications of the medical record numbers, date of birth. There are no interruptions or distractions during this time. Every center has its checks and balances in place because this would be a big error if it happened.

Mary DeRome (MMRF): Yes, I would say.

Don O'Connor: We're not trying to jinx me, I hope.

Mary DeRome (MMRF): No.

No, we're not, we're not. It sounds like you're getting ready to have a transplant. Are you planning on having one?

Don O'Connor: No, but we did stem cell harvesting right at the 1st of the year, in case in the future we need to do it.

Mary DeRome (MMRF): Okay, good to know. Is that part of the protocol for the clinical trial that you're on?

Don O'Connor: Yes, the trial, in my mind, the way that I explain it to myself, is that it's kind of a performance-based trial, and as long as I'm performing according and my numbers are meeting targets, the goal is to give me as little bit of medicine as possible to get me where I need to go. That way, the side effects are minimal and there are options for the future. As long as I met my targets along the way, with the biggest target finally being an MRD-negative reading.

Once I got to that point, I was able to get out of induction and then move to the next phase, which was going be either harvest your stem cells and keep them and freeze them, or take them out and put them back in after the chemo. We're sitting here now with a couple 15 million stem cells at the blood center, and we're waiting, hopefully, to never use them.

Mary DeRome (MMRF): Luckily, they last for a long time, so, you'll be able to use them in years, if you ever need them. It's a good thing to have in the bag.

Don O'Connor: Yes.

Mary DeRome (MMRF): Dr. Kaur, you talked a little bit about eligibility criteria, so we don't have to go over that again unless you want to. But if you're found to not be eligible for a transplant, what do you then treat patients with?

Gurbakhash Kaur, MD: Then we treat based on the MAIA trial, with the Darzalex-Revlimid-dexamethasone (DRD). That's the standard of care in the US. These patients tend to be elderly, so I try to spare them Velcade, especially given the neuropathy risk with it. My go-to regimen is DRD. Now, of course, when I get frail patients, I would start with one drug and I would add if needed. You assess the patient in front of you, not necessarily an algorithm that you follow. So DRD continuous treatment is what we follow for the transplant-ineligible or deferred transplant approach.

Mary DeRome (MMRF): Okay, so let's move on and talk a little bit about maintenance therapy and MRD testing. Dr. Kaur, Don mentioned that he was tested for MRD, after his induction therapy was complete. We're going ask a few questions about MRD.

Basically, what is MRD testing? And do you have to get a bone marrow biopsy to get tested?

Gurbakhash Kaur, MD: MRD is minimal residual disease; it's currently the deepest way of assessing response. I use an example of the iceberg. You see what's on the surface, and then you don't see what's underneath. And bone

marrow, when we say somebody has a complete response (CR), or an stringent CR (sCR), we're not totally at the deepest level of assessing the response.

Currently, it's mostly in clinical trials, but MRD obviously is moving to clinical practice. The implications are still being debated within the myeloma community, but 10^{-5} or 10^{-6} is usually what we go for. And we use next generation sequencing (NGS). There's two ways to do MRD assessment, one is flow cytometry-based and the other one is NGS-based. And we use the NGS method. Don had it after six cycles, and he was MRD-negative, so he did not have to have an escalation or addition of a fourth drug, so he deescalated.

For my patients who are MRD-positive on this trial, I add a fourth drug, Velcade, and we do that for a certain amount of time, then reassess the response. If it's MRD-negative, we deescalate. If it's MRD-positive; that's when they go for transplant. It's a risk-based assessment, and currently, my first assessment is usually post-transplant, to assess the deepest level of response they have achieved. Then I monitor them periodically.

Yes, you do need a bone marrow biopsy. In certain patients, I have done blood-based NGS testing, and I have some preliminary data on that, on a very small cohort. But you may not have enough disease in the blood to be sure.

Mary DeRome (MMRF): Yes.

Gurbakhash Kaur, MD: Yes, peripheral blood is not the most reliable, because if it's negative, it doesn't tell you a whole lot. If it's positive, it tells you that you're going to relapse. The go-to site of testing is actually bone marrow.

Mary DeRome (MMRF): If a patient was going to a community practice or a standard doctor's office or a hematologist-oncologist in the community, is MRD testing more of a standard there, as well, or not yet?

Gurbakhash Kaur, MD: No, I think it is still mostly used in academic centers. I often tell people that our goal is to get MRD negativity, but it has to be sustained MRD negativity.

The information that I'm gathering from MRD negativity is not going to make me not put you on maintenance therapy or deescalate that. One of the biggest challenges in myeloma is, actually, we don't know which patient to continue therapy on and which patient to deescalate therapy on. I really think that MRD will have a space in that. If you have sustained MRD for a couple of years, there was an abstract that alluded to this, then possibly you could consider deescalating. I think that's where the role is, but mostly, it's done at academic centers.

Mary DeRome (MMRF): I saw that at the American Society of Hematology meeting (ASH). It'll be interesting to see what these studies are going to show about discontinuation of therapy after achieving MRD negativity. But MRD negativity really is the goal of therapy, at this point. If you can administer the test and you see that you're getting a negative result, then basically, you've achieved your goal, at least in the short-term.

Gurbakhash Kaur, MD: Yes that would be the goal. We have to be practical. What happens at academic centers cannot always be applied to community centers. Reimbursement for the test is a big challenge, as well. For that to become widespread, there has to be solid data, and I think that's what the myeloma community is trying to figure out.

Mary DeRome (MMRF): Yes, insurance is a huge issue. We don't talk about that enough, but, you have to deal with that on the frontlines all the time, and it's hard.

Gurbakhash Kaur, MD: Yes, it is very hard.

Mary DeRome (MMRF): Sonia, aside from MRD negativity, can you tell us what other responses to induction therapy patients might achieve? And then, how is response to treatment traditionally measured?

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: We typically follow criteria by the International Myeloma Working Group. We'll look at how their markers have responded to therapy. Dr. Kaur just mentioned complete response for that matter. That's when, after treatment, we've noticed that there is an absence of the monoclonal (M) protein in both the blood and urine. There's no soft tissue plasmacytoma. If they've had a bone marrow, it's less than five percent involvement. If we're following their free light chains, then it's a normalization of that ratio, in addition to the criteria. To make this astringent complete response, it's all of these criteria, plus, having no clonal cells by bone marrow aspiration.

For those who have had a very good partial response, we're seeing a 90% reduction in either blood, urine, or monoclonal protein. And again, if we're following their free light chains, it's greater than 90% decrease in the difference between the involved and uninvolved free light chain levels.

Then there's partial response, where it's more of a 50% reduction in the M protein in blood and urine. Or if they've had at least 30% plasma cells in their initial bone marrow, we're seeing at least a 50% reduction post-induction therapy. Then minimal response is even a little bit further down where it's between 25% and 49% reduction. Lastly, there's stable disease where they don't meet criteria for any of the above, and it's continuing to be about the same.

Mary DeRome (MMRF): So, Don, are you on any therapy right now? And if so, what are you on? And then, let us know, how you are feeling.

Don O'Connor: Yes, we're in the maintenance section of the trial. I'm still doing the same three drugs from the original induction phase, except, a lot less dosages of each of them. Now I do Darzalex and dex every 2 months, and I still do Revlimid every 21 out of 28 days, except, it's a reduced dose of that as well.

Because of the fractures, we've added in Zometa, and that's an every-month, as well. So, it's much better now than going every week or every-other-week; I get to stretch it out to every month.

Mary DeRome (MMRF): Well, sure, I can imagine.

Don O'Connor: Yes.

Mary DeRome (MMRF): Good. Are you feeling any side effects from what you're taking right now?

Don O'Connor: This month, no. That's maybe one of the harder parts, now, is that, for me, each different month, I would never know. Sometimes it's constipation; for January and February it was really dry skin, which I'd never had before. But there's plenty of different potential side effects, and I imagine I'm going to run through them all before it's over.

Mary DeRome (MMRF): Maybe.

Don O'Connor: I think the thing that got me more excited than anything was that, from the time we started treatment, I could feel myself getting better. Almost every day I felt, "Well, I feel better than yesterday," and you do that for months and you really get a really good positive outlook.

To the point where, I got a call from one of the local support groups, because I signed up for it but I never did anything with it. And he called and he said, "Well, you know, you're on the list, but you never join in or do anything." I said, "I'm just selfish, because I really don't want to know what's going to happen. Because I feel so much better than yesterday, I don't want you to tell me that in a year it gets worse. I don't want to know that, because I'm so much better than I was."

Mary DeRome (MMRF): I can see that.

Dr. Kaur, what Don is on for maintenance is not really what you would say is standard of care. He's taking Revlimid, which is the standard of care, but then he's on a couple of other things, too. This is probably just the result of the clinical trial that he's on? Which really prescribes what he should be taking at each step.

Can you talk to us a little bit about maintenance therapy and some of the standard of care? We know there's an approved standard of care but there's also other regimens that people use for maintenance.

Gurbakhash Kaur, MD: Yes, Don is on the maintenance regimen per the trial, and he's going to get an assessment once he completes this. If he's negative, he's going to move on to probably only one drug of that regimen. Traditionally, the standard of care is actually Revlimid, 10 milligrams continuously; that is usually what ends up being given as maintenance therapy. Oftentimes, we have to tweak the doses based on tolerance. Many patients, post-transplant, actually have a very hard time tolerating Revlimid due to cytopenias or GI toxicity, so you end up, tweaking the doses, possibly 10 milligrams for 21 days, 7 days off, sometimes even dropping down to 5 milligrams, you can do that.

Some other regimens that can be used for maintenance therapy but are not as common include Velcade, particularly if they have a t(4;14) translocation. I try not to do Velcade-based maintenance as much as I can, because many patients end up getting neuropathy from Velcade. I think that's actually one of the most challenging side effects to deal with in respect to the myeloma patient's journey with myeloma. They live many years and the neuropathy is the most bothersome.

I don't do twice-weekly Velcade, I also do only once-weekly Velcade, for that reason. Although the data behind doublet-based maintenance therapies is not so solid, but it has been done in clinical trials such as FORTE and GRIFFIN. In a selected patient, depending on how many high-risk cytogenetic markers they have, usually, those are the patients you would consider a doublet-based maintenance therapy. Or even patients who have sort of primary refractory myeloma, those are the patients I would consider. But generally, the go-to thing is Revlimid.

Mary DeRome (MMRF): Speaking of Revlimid, Sonia, Dr. Kaur said that patients often have trouble with taking Revlimid and they have some bad side effects from that, especially cytopenias, low white blood cell counts and low platelets while on therapy. What can you offer patients who have these side effects from Revlimid?

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: We often have to give a granulocyte colony-stimulating factor, so in other words, we're stimulating the white blood cell. Or platelets get too low, then we're having to hold the Revlimid along with the anticoagulant that they're on.

We do use sort of a stepwise approach. If we feel like these dose interruptions are happening more frequently, we'll go from 10 milligrams continuously to just 21 days, or we'll further dose-reduce to 5 milligrams. And we can even extend the cycle to 35 days, so offering a 2-week break rather than just the one.

Mary DeRome (MMRF): Okay, that's good. Dr. Kaur, let's talk a little bit about second primary malignancies with long-term use of Revlimid. There were several talks about that, at the recent ASH meetings back in December. Are all patients who are on Revlimid maintenance at risk of these second primary malignancies?

If so, is there anything that can be done to lower that risk? From what Sonia was saying, the timing of the maintenance, taking breaks from treatment, or dose reductions of Revlimid does that actually help with that?

Gurbakhash Kaur, MD: I think it's not just Revlimid alone; I think it's possibly the combination of melphalan and Revlimid, because melphalan is an alkylating agent. I think the combination of those probably increased the risk.

When we counsel patients on maintenance therapy, we discuss all these possibilities, and you're at a difficult place at that stage, because you want this cancer to stay in control. You don't necessarily want to worry about the next one. But we do a very good job of basically guiding the patient in terms of screening, so make sure that their colonoscopies are done, mammograms are done. They're going to the urologist. They're going routinely for their skin care check, and going to their dermatologist.

Sonia and I have a very holistic approach to this. We can't prevent everything, but we try to stay on top of the healthcare maintenance part. Most of the time, oftentimes, more than the primary care, sometimes, we're on top of it and we're telling the patient, "You need to get your colonoscopy done," or, "You need to get your mammogram done." We try to counsel it that way.

Mary DeRome (MMRF): Okay, that makes sense. My final question for all of you is what advice would you give to a myeloma patient who was navigating initial treatment options? Don, I'm going to let you answer first.

Don O'Connor: I would say to find a clinic or a hospital or at least find a doctor that's really familiar with multiple myeloma. I think, as you said, the clinic or UT Southwestern having some different resources than what some community centers would have, I think that's a great option to add to your thing. Then the other one is to watch out for all of the statistics. Once you start doing your research when you first get diagnosed, there's all kinds of things you'll find on the Internet.

Mary DeRome (MMRF): Yes, sometimes better not to look, right?

Don O'Connor: Right, but you're going to find it, once you find it is when you quit looking. I don't want to know those anymore. But the thing is that the statistics are old, because it takes a whole range of time to create.

Mary DeRome (MMRF): It's true, it's true, it really is, and even the ones that people use routinely, like the government statistics, etc, they're only up to 2018 or something. And that's already five years ago. A lot happens in myeloma in five years, so it takes time for the statistics to catch up with the therapy advances that happen in myeloma literally every year.

Don O'Connor: Yes, and the other one is, you're going to end up cashing in all of the good will and all of the honey-dos that you've done in your life, with your caregiver, because they are so important to the process. Like I said, my wife is not here. We're on vacation and I didn't have enough medicine, so she's gone to the Walgreens to get it filled while I'm here with you guys.

Mary DeRome (MMRF): Excellent, that's a great story. Caregivers really are important. So, so helpful.

Don O'Connor: Yes.

Mary DeRome (MMRF): Sonia, what advice would you give regarding navigating initial therapy, for a newly diagnosed patient?

Sonia Patel MPH, MSN, APRN, AGACNP-BC, AOCNP: I think it's important to keep in mind, although there's currently no cure for multiple myeloma, there's so many treatment options, and overall, the prognosis for someone diagnosed with this type of cancer has dramatically improved over the last several years.

Patients are living longer and it's really truly like treating a chronic disease now. But given this, patients need to understand that they will be always on some sort of therapy. Even if they do go through induction therapy, have a transplant, and our maintenance therapy about three months post-transplant, patients can sometimes struggle having to go back on some kind of treatment at that point.

But it's really these agents that are helping lengthen their remission or deepen their response, and keep the disease well controlled.

Mary DeRome (MMRF): Okay, Dr. Kaur, the last word, what is your advice?

Gurbakhash Kaur, MD: Well, first, I want to thank Don for joining. This is a great service that you're doing while you're on vacation, so we are very appreciative of that.

Mary DeRome (MMRF): Yes, absolutely.

Don O'Connor: You're welcome. I owe you way more than this.

Gurbakhash Kaur, MD: Aw – thank you.

Don O'Connor: You're welcome.

Gurbakhash Kaur, MD: I think the main message is don't be afraid to ask questions. And you should never feel bad about getting a second opinion. I tell that to my patients, "It never hurts my ego if you go and get a second opinion, because it's your body." I think getting a second opinion, getting another person's perspective on your disease is always something to go along.

All the things that Sonia and Don mentioned, that caregivers are important, this is a chronic disease, there's lots of therapies, there's a lot of hope in myeloma. We were at a point where we didn't have good therapies, now we've got them. Well, now maybe we're overdoing it and maybe we're underdoing it. And that's the process where I think we're going make the biggest impact in terms of research, who are the patients we deescalate therapy, who are the patients we escalate therapy. And I think this is where the future is going to be.

Mary DeRome (MMRF): Yes, I agree. At this past ASH, there were a number of studies which were looking at de-escalation or even stopping therapy all together, after a number of years of being on maintenance, etc. We'll see how the data plays out. It'll be interesting, considering all the new therapies that we have. It certainly is a very hopeful time in myeloma, there are certainly many, many options for patients, which is a great thing.

So, on behalf of the MMRF, I'd like to thank Dr. Kaur and Sonia Patel and Dennis O'Connor for joining us today for this Facebook live.