FAQs on Multiple Myeloma Following Relapse After One to Three Prior Lines of Therapy

July 28, 2022

Transcript

Mary DeRome (MMRF): Welcome and thank you for joining us for today's session, *Frequently Asked Questions on Multiple Myeloma Following Relapse After One to Three Prior Lines of Therapy.* I'm Mary DeRome, Senior Director of Medical Communications and Education at the Multiple Myeloma Research Foundation. Today I'm joined by Dr. Andrew Yee and Ms. Stephanie Sanford from the Massachusetts General Hospital in Boston, Massachusetts, and John Selin, a multiple myeloma patient from Georgetown, Massachusetts.

We've invited them here today to answer some of the frequently asked questions we've received from patients and caregivers about early relapse from treatment.

Dr. Yee, I'm going to start with you. How do you know if a patient has relapsed from treatment?

Andrew Yee, MD: That's a core question that emerges. When I think about myeloma therapy, I think about how, when patients are first diagnosed with myeloma, there's a lot of drama, for lack of a better term.

They're thinking about what they're going to do. Myeloma is a diagnosis typically of people around the age of retirement. When a patient gets told about this new cancer diagnosis, it turns their life upside down. They have to meet all these new people, hear about treatments, and learn this whole new vocabulary. It's a big imposition on their lives.

But once they get over that hump, most patients hit a stride, so to speak. After the warm-up period, the majority of patients put in a lot of work in that initial course of therapy. The majority of patients get the dividends back in terms of feeling better, and you get the immediate gratification from looking at the labs and you see them looking better. That looks great.

There's a lot of work put into visits, dealing with side effects, and just navigating through all of that. Now, for the majority of patients, the initial therapy works well for months to years. You get to a point where, for the majority of patients, after the initial course of therapy, they're on maintenance therapy where the disease is in check and they're on a pretty stable regimen. People are thinking about moving on with their lives and their next steps. Myeloma goes from being on the front burner to, for many people, the back burner. You think about it intermittently, but hopefully for the majority of people, it's not front and center all the time like it was when you first got the diagnosis.

Now the thing about myeloma is that it's not curable, but it's very treatable. But because it's not curable, the disease does tend to show up again over time. For many people, we can put it into remission where it's under control, it's not active—I think of it as being in hibernation. But over time, the disease can come out of hibernation. That would be what

I think of as a relapse. We might be touching on this later, but maybe this would be a good time to talk about how is relapse defined?

Typically, when I see a patient, I always ask how they're doing, how are things going on the therapy, just to make sure, because side effects can emerge on treatment. But we also do like routine laboratory studies to check on the status of the disease.

The routine laboratory studies is typically when Stephanie and I see a patient. John can acknowledge this, too, because he knows; he gets lots of tubes drawn. We always check the myeloma-related labs, which include the serum protein electrophoresis and the serum free light chains to monitor the disease. For most patients, those numbers are pretty flat or stable. But an indication that relapse is occurring can be when the numbers start to increase.

If the numbers are starting to increase, we start to think, "Okay, maybe the disease is more active; the disease is coming out of hibernation." Now, just as an aside, it also depends on if a patient is participating in a clinical trial or not, because it turns out that there can be more formalized definitions of relapse in terms of the actual magnitude of the increase. Some patients can have a small, very gradual increase in monoclonal protein that may or may not be clinically important or something to act on that maybe you can just watch very closely.

For the purposes of a clinical trial, if for example, monoclonal protein increases by 0.5 g/deciliter from the best response, that could be considered evidence of a relapse, or if the free light chain increases by 100 mg/L in patients who do not have measurable serum protein electrophoresis. That would be a clinical relapse where a patient, for the most part, is feeling well, but has a relapse mainly based on these changes in monoclonal protein or serum free light chain. That wouldn't be how I define a biochemical relapse.

Most patients have frequent visits just so we can see how they're doing. But for most patients, we can see that based on the laboratory studies alone.

Mary DeRome (MMRF): It seems like you're saying that some patients have what you might consider to be a more rapid increase in those markers. M protein or light chains, but other patients have these numbers creep up a little bit. So, the rapid increase is more concerning than the creep?

Andrew Yee, MD: Yes, exactly. The magnitude of that is important. There can be a little bit of a gestalt to it, as well. Sometimes there's a formalized definition and sometimes it can be more of a gestalt, and it gets to how—this is a corny joke—multiple myeloma is multiple in the sense that there are multiple types of myeloma in terms of their clinical presentations.

When you first meet some patients, their myeloma is defined because they have a bone lesion, have kidney trouble, or low blood counts. The way they present, and the variability and heterogeneity of how they present, could also materialize in how the disease was to show up again. This can be pretty heterogeneous, as well, and you can really see a divergence in what the disease looks like at that time.

Mary DeRome (MMRF): Stephanie, we're talking about monitoring patients when they come in for their regular scheduled appointments. How often are patients monitored? There are tests like blood tests, urine tests, imaging tests. To ensure that a patient stays in remission—or to detect any possible relapse—how often are these patients monitored?

Stephanie Sanford, MS: Myeloma is easier than some other diseases to monitor, because we can see what's going on most of the time in the blood. It can vary across practices, but typically—the way I practice—is we see people about once a month. That way we can check on how they're doing and how they're feeling. Sometimes part of that visit is getting those labs, mostly blood drawn, to see whether things are stable. Sometimes those visits are really quick. When the labs look stable, everyone looks good and it's great, our check-in is fine.

We're able to see a lot and monitor patients easily in the blood. Our cadence while people are on active therapy—no matter what line of therapy it is, relapse or initial—is that I'm going to see a patient at least once a month, sometimes twice a month. But those lab markers we're going to draw once a month. I'm not sure it's clinically indicated to draw them more often than that. Once people get off active therapy and onto more of a maintenance therapy where we know the disease at least at some point has been under control, once we get a few months out from that, we can pull back a little bit.

It might be their genetics that they initially presented with. If they have anything else going on, we can pull back to every 6 or 8 weeks. In rare instances we pull back to every 12 weeks if people are really stable, or if other things are going on in their life that they're dealing with—knee replacement surgery or something like that—and we can put the myeloma on the back burner so they can manage some of these other things.

Imaging is another question that comes up frequently. Because we can see so much in the blood with just the needle prick, we often don't do a lot of serial imaging—and we try not to. Often, at times of relapse, part of that workup will initially be imaging. But if a patient is showing clinical improvement on treatment, they're not having any side effects or pain or issues anywhere else, often we won't do a lot of serial imaging. If disease is under control or maybe not in a full remission, but close, we might not. However, we do have a very low threshold to do any imaging, if any clinical issues occur. A shoulder that's had arthritis for 5 years that all of a sudden changes—I'm going to get imaging right away, but not really just serial just to monitor.

Urine studies can sometimes be helpful, but I'm not going to make clinical decisions based on urine studies by themselves. We might watch patients with kidney disorders or kidney issues and interpret that along with all of the other things that are going on. But the urine results and the urine testing is becoming less important over time.

Mary DeRome (MMRF): It sounds like patients that are on maintenance and stable might be coming in to see you less frequently. But that may not be the case when they're on initial therapy or maybe after they relapse and have to go on a new therapy. You would have to see them more frequently because of those things.

John, can you tell us how you found out that you had relapsed? Could you tell that you had relapsed without seeing test results?

John Selin: Both ways. It's been 18 years since my original diagnosis, I've been on four lines of therapy, and I've had three relapses over the years. For the last 5 years I've been with Dr. Yee and Stephanie. They've been a great team helping me out, getting me into a good position. But my original line of therapy 18 years ago was an autologous stem cell transplant (ASCT); that worked out very well.
The maintenance at the time, 18 years ago, was just bone strengthener infusions, and that was going for 8 years. I'd be monitored with lab tests maybe every 3 months.

But all of a sudden, the IgG levels in the blood tests were going up. At that time, they weren't really monitoring light chains yet. Every once in a while they got tested but not on a regular basis. That was the first relapse. Then, 4 years later—8 years after the original transplant—I was on Revlimid, and of a sudden I was getting pains in my side. I thought I'd bruised my ribs. My primary care doctor did an x-ray, and said, "Gee, it looks a little funny." It was sent to my oncologist at the time, who immediately did an MRI and could see that I had lesions growing on the outside of my spine.

They were extramedullary lesions, which were treated. At that point—2 years later—I had treatment. And then 2 years after THAT I had shoulder pain. All of a sudden the shoulder was hurting every time I moved. X-ray and MRI showed that the primary problem was that I had broken my clavicle, but the MRI showed lots of lesions in that scapula area. At that time I went on the line of treatment that I'm on right now, and it's working very well.

Mary DeRome (MMRF): You did feel it, so it hadn't come as a shock because you thought something was going on, right?

John Selin: Right. The blood tests, in each case, were showing some rise, so there was confirmation.

Mary DeRome (MMRF): Dr. Yee, can you explain the difference between biochemical relapse and clinical relapse? Are there other terms that patients hear, such as early relapse or aggressive relapse? Does a patient's cytogenetic profile—meaning what's happening with their chromosomes, translocations and deletions—factor into these definitions?

Andrew Yee, MD: John's case is really remarkable: in 18 years, he's really seen the really amazing developments of myeloma therapy, and he's really benefited from that. John's case also demonstrates the difference between biochemical and clinical relapse. When John mentioned that he had the rising IgG, it was mainly laboratory-based tests, and that is the biochemical relapse.

But when he had the rib pain and the rib issues or the spine issues, then that is more a clinical relapse, where you can see the myeloma actually causing symptoms or some clinical evidence of disease besides the monoclonal protein studies of the light chains. When I think of clinical relapse, I think of the bone lesions, or some patients are going to have new anemia or thrombocytopenia that's out of proportion to what was going on before. Or somebody developing kidney problems related to the disease: that would be more clinical relapse.

As a side note, the majority of the time, clinical relapse is associated with evidence from the laboratory parameters. Usually, patients have a clinical relapse, and you can see evidence of that in a rise of clinical protein or light chains.

A couple points to emphasize: we're more sensitive if a patient reports that his rib hurts and his back hurts. Our ears perk up a little more. It can be complicated, because a lot of people have back pain. But I always wonder, is that related to myeloma?

That's why our threshold for ordering a CAT scan for myeloma is lower; we want to confirm if it IS related to myeloma. Very rarely, patients have disease progression with new bone lesions without a change in the monoclonal protein. That can happen, but that's less frequent. Their relapse can be nonsecretory—as in, you don't see the myeloma maker. That can happen later, as the disease evolves, but I'd say it's probably under 5% or 10% of cases.

That relates to the frequency of the imaging. Patients who have a nonsecretory relapse I do monitor with imaging more frequently, but as Stephanie was saying, typically we don't necessarily monitor patients routinely with imaging. But something else to appreciate is that there's a lot of heterogeneity in practice.

There's not really one right answer here. There's not a right answer. It's not one size fits all. In terms of early versus late, early relapse implies that the disease relapses in a shorter timeframe than average. When you think about initial therapy in myeloma, generally speaking, people have a runway of about 4 to 6 years on average from the initial therapy. So something less than that could be considered an early relapse. But for the purposes of some of the clinical trials, sometimes people think about within a year of ASCT or within a year and a half. That could be one definition that's being used by clinical trials, because there are clinical trials looking for patients who have a so-called early relapse.

Regarding the question about FISH and cytogenetics: *FISH* refers to fluorescence in situ hybridization; *cytogenetics* refers to the myeloma's chromosomes—under the hood of the myeloma cell. How are the chromosomes attached to each other? The chromosomes are the instructions that tell the cells how to divide. There can be configurations where the instructions short circuit. It's kind of rearranged—the instructions get scrambled. It can short circuit how the cells behave. There are certain chromosomal abnormalities that can be detected by FISH that can be associated with a duration of response that may not be as long as is seen in the average patient.

The classic ones we think about are translocation 4;14, translocation 14;16, and deletion 17p—where part of chromosome 17 is missing. This refers to in the myeloma cell. It's not something that you're born with. It's something that the myeloma cells acquire as part of becoming a myeloma cell. Recently, we also associate gain or amplification in 1q.

We are starting to pay more attention to these. It can influence the type of initial therapy, as well as the maintenance regimen. Sometimes it provides, in patients with a relapse, insight into choosing one therapy versus another therapy. But again, this is really a moving target.

Now I should also say, there are also patients who can have an earlier relapse and still have normal cytogenetics. Stephanie and I definitely have plenty of patients who do not

have high-risk FISH but whose duration of response does not last as long as we would like.

Mary DeRome (MMRF): Stephanie, pretty much every myeloma patient is going to relapse, right? How many times do patients relapse? If you're one of these people who has a shorter duration of response to a treatment, do you relapse more frequently from subsequent treatments?

Stephanie Sanford, MS: It's a really tricky question, given the variety of patients that we have and the variety of ways people present. Sometimes the initial treatment produces a remission that lasts up to 5 years. This is a disease largely of an older population, so if someone's coming in at 85, 90 years old and they get a great first remission, they might not relapse. They might have other health problems that come up in the future while the myeloma's on the back burner. That can almost be the best-case scenario, where you get these long remissions.

If you're 80 and then 10 years later something happens, the myeloma isn't the biggest deal. There is that other side that some of the tougher, more aggressive diseases that Dr. Yee was describing—sometimes we can predict based on how they present or on genetic changes.

Sometimes we can't predict when people can relapse more quickly, multiple times. It can take a few tries to get them into remission as opposed to responding right to that first therapy, like we're getting used to expecting, because we are often able to see that now.

There's no number of times somebody can relapse. Sometimes, as the relapses go on, these remissions get shorter with each time. We do have patients who go from active treatment to active treatment and don't have any, or a long time of, remission in between. Thankfully for that population, and moving forward for even people who have long remissions, we're finding new treatments all the time.

Every day, new things are coming out. So, we're able to keep switching therapies and having so many more options than we did when John started this, so many years ago. I have some patients going through three lines of therapy in a year or two, and here we are 18 years. In that 18 years, there have been 20 other lines of therapy that have been created. We're in a much better place overall, but there can really still be a tough spot when you're finding that frequent relapse.

Mary DeRome (MMRF): John, you mentioned that you've had four relapses.

John Selin: Three relapses, four lines of therapy. Fourth one is still going well.

Mary DeRome (MMRF): When you relapsed and went onto another line of therapy, did you have any expectations about how long your response to that would be? Do you follow the lab results that you get whenever you see your care team?

John Selin: The answer to that last one is, yes. The lab results, as soon as they come up, I get notified on the patient gateway, and I take a look as they come in. But in terms of expectations, certainly after the initial treatment, the transplant, and 8 years in remission, it was like, maybe I don't have to worry about the myeloma. I knew it wouldn't be cured, but it was like, I don't have to worry about it anymore. So, when things started

rising again, the IgG levels, it was okay. It was a shock, and I said, okay, I do have to worry about it.

I knew there would be relapses. Talking with the doctors at the time. Also, I would see the results. I would follow the major hematology and the different conferences and the webinars where you see the trials, and you see that patients do start to fall off as the line goes down so that years are good expectations.

My second line of therapy was 4 years before the relapse, so I felt good that I was responding well. I've been very fortunate that my responses to each line of therapy, when we had to change, were good.

Right now, the fourth line of therapy has been 3½ years, and it's still going well.

Mary DeRome (MMRF): That's great.

Dr. Yee, many patients are treated with multidrug regimens; patients are never, or only rarely, given one thing at a time, is that right? If a patient relapses after being on multiple drugs at one time, is there a way for you to tell which of the drugs is no longer working? If so, would you then just swap it out for a different drug in the same class or just move on to another treatment?

Andrew Yee, MD: That's a question with some nuanced answers, I think.

If a patient's on a three-drug regimen and the disease progresses, it can be challenging to know exactly which drug is no longer working. Sometimes you never know. So, there are different layers to this.

For example, in the typical case, somebody who's on one line of therapy—say they had initial treatment with lenalidomide, bortezomib, dexamethasone and RVd; they had a cell transplant and then they're on lenalidomide, like Revlimid maintenance. Then the patient experiences some relapse. The question becomes, what choice of therapy do you do next? In 2022, we have all these different options you can choose from. So, for some patients, my bias would be if the patient has not had seen an anti-CD38 monoclonal antibody, that would be a good time to think about using an anti-CD38 monoclonal antibody. The choice could be daratumumab or isatuximab.

Then we're talking about partnering these drugs to get maximal benefit. Sometimes you can think about combining it with pomalidomide or a drug called carfilzomib. That's a common question. It really depends on the patient's situation, because the regimens are different. The scheduling and the side effect profile can be different.

If a patient progresses on lenalidomide then switches to pomalidomide, even though it's the same drug class, it still has activity. In that case, the pomalidomide is still an option. And carfilzomib is also a great drug to consider, but it's administered intravenously and has a different side effect profile.

A lot of patients have a love/hate relationship with dexamethasone. Some people love it. Some people hate it. We talk about swapping out things. Dexamethasone is a pretty common thread throughout almost all myeloma regimens. That's because dexamethasone accentuates the activity of the other partners.

In some patients, if the relapse is gradual and not aggressive—maybe it's just the numbers are changing a little bit—sometimes I have just used daratumumab by itself for those particular patients. if a patient progresses on that, sometimes you can actually see activity with adding on a drug that they've had before.

There can be some synergy between, say a CD38 antibody and lenalidomide, pomalidomide, or a proteasome inhibitor. But a lot of it can depend on the scenario in terms of the type of relapse and what the patient has seen before.

But I also see cases where, if somebody was on daratumumab, pomalidomide, and dexamethasone, for example, and if that treatment is no longer working, I can see situations where you can replace all the components completely, where you would do carfilzomib, say cyclophosphamide, would be one example.

There are all these variabilities. A lot depends on the scenario. Some patients, if it's a gradual, maybe you could just swap out one of the drugs, but if it's something that needs more, you might swap out more.

Mary DeRome (MMRF): Now we're going to talk about treatment options for relapsed patients who have had up to three lines of prior treatment.

Dr. Yee, there is still confusion about what constitutes a line of therapy. What is a line of therapy? For example, if a patient had RVd followed by stem cell transplant and then Revlimid maintenance, then they relapsed and were put on a different triplet regimen, how many lines of therapy has that patient had?

Andrew Yee, MD: Technically, if someone is on the initial therapy plus a transplant, that's considered one line of therapy. If you were to change out the treatment because of disease progression, then that becomes your next line of therapy.
It can be confusing, because they're on three different drugs in the beginning.

Sometimes how we define relapse gets tricky. Is it really important? Is it really the number of lines of therapy, or is it really the types of therapies that you've had? So, there's increasingly an appreciation that it's also the types of therapies that you've had that is important, too, not just necessarily the number of therapies.

Mary DeRome (MMRF): So, it's really more of a drug class issue?

Andrew Yee, MD: Right. So, you've had a CD38 antibody therapy. A lot of the clinical trials, when people report out results, they're talking about triple-class exposed or refractory. Triple-class exposed would be having had an immunomodulatory drug like lenalidomide, a proteasome inhibitor like bortezomib or Velcade, and then the CD38 antibody like daratumumab or isatuximab. It gets a little tricky. There can be a gray zone in terms of the package insert and insurance. There can be some variation in interpretation. Whereas in a clinical trial, it tends to be pretty formalized in definition for lines of therapy.

Mary DeRome (MMRF): Sometimes a patient is taking three drugs and begins to have some side effects from one of the drugs. There might be a dose reduction in that particular drug; would that be considered a different line of therapy?

Andrew Yee, MD: If somebody had a dose reduction, that would not be considered a line of therapy. If somebody was on RVd in the beginning, and then the Velcade was discontinued for neuropathy and then changed, then you had to change to carfilzomib, for example, that would probably be considered new line of therapy. I might have to double-check that.

In terms of swapping out treatments, I have patients where I have replaced bortezomib with carfilzomib and seen beautiful responses subsequently.

Sometimes it's helpful to change all the drugs and sometimes it's not necessarily best to change all the drugs.

Mary DeRome (MMRF): Stephanie, is a stem cell transplant a treatment option for patients at relapse, even if the patient has already had one? What are the chances that a patient might not respond to a transplant at relapse?

Stephanie Sanford, MS: This is a controversial topic.

A lot of the clinical trials that have shown that transplant is a great option for myeloma patients were done before we had a lot of these new therapies that we're feeling confident are giving us long sustained responses, with patients coming in weekly or three weeks out of the month for treatment versus interrupting their lives for month-long hospitalization, for lots of appointments 90 days after or 30 days after—the concerns of the mortality and morbidity just associated with the actual transplant itself.

That being said, here's John as a great example of someone who had a transplant right off the bat, not at relapse, and did fantastic with it. So, any time we talk about transplant, we have to take some of that information into play.

Transplant's always an option, almost always. So, we just have to figure out where in the line of therapy we want to put it. I don't see a lot of second transplants being given, and that's for the reasons we were talking about: we have all these other new promising drugs to try that aren't going to interfere and give quite the toxicity that the transplant would. But we still do have plenty of patients that we are giving transplants to. So we are still doing that, and we have a minority of patients that are going on to transplant right now.

Sometimes the up-front transplant will give you a little bit more. Studies are showing that that might give you a longer remission, starting up front. That said, we don't know. Sometimes when we do it a little later on, we get a great response, as well.

So, we really use transplant almost just as another line of therapy and throw it all in there. When we see how easy some of these newer lines of therapies are, a lot of people are opting for that.

Mary DeRome (MMRF): We've talked about the DETERMINATION trial in some of these events that we've had since ASCO. It's going to be interesting to find out if they do a similar study with some of the newer regimens, some of these four-drug regimens that are really very effective in the up-front setting

Mary DeRome (MMRF): John, what can you tell us about the treatments you've been on? What lines of therapy have you been on since you were diagnosed? What responses did you achieve, and what are some of the side effects that you've had?

John Selin: As I've said, 18 years ago initial treatments were completely different. Similar in some cases, but what was available then was not the same as now. Initial treatments with Thalomid, the precursor to Revlimid. Also, with dex and bone strengtheners. But I also initially had radiation treatment for lesions in my back. I had kyphoplasty to shore up three of my crushed vertebrae in preparation for the transplant.

But the side effects, I had a lot of bone pain. It was really intense bone pain. So, I was on a lot of pain medication, and the pain medication leads into side effects. I was taking a lot of other medications to alleviate the side effects. A lot of stuff was going on during that time.

The biggest problem during that initial treatment was the peripheral neuropathy in my feet and my fingertips and that, due to the Thalomid. That gave me an impetus to say, okay, the neuropathy is going to get worse probably over time. Let's do the ASCT. That was the primary reason we're going to do this transplant.

Mary DeRome (MMRF): At the time there really wasn't much else, right?

John Selin: Exactly.

Then, as I said, that was good for about 8 years. Then the next line of treatment was Revlimid, and that was for about 4 years. Then, after there was a relapse, the next treatment was Velcade. By that time, it was subcutaneous, which supposedly would have fewer side effects or less neuropathy, than the infusion. I also was taking Revlimid with the Velcade, and then I relapsed. Now I'm on a triplet: daratumumab, dex, and Pomalyst. I actually switched over to Pomalyst, I think back to Velcade, also when that was available.

For 3½ years I've been feeling well. On the lab tests, everything looks good. We'll just keep on going. Unfortunately, the neuropathy is still there.

Mary DeRome (MMRF): Dr. Yee, there are many options available for patients who've relapsed from one to three prior lines of therapy, including drugs from many classes, like immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies with most of the newer agents like CAR T cells and antibody-drug conjugates reserved for relapse after four or more lines of therapy. With all of these options, how do doctors decide on a treatment to give a patient at early relapse? And what should a patient tell their doctor during this decision-making process?

Andrew Yee, MD: The choice of therapy at time of relapse can be pretty complicated, because for initial therapy, there may not be as much heterogeneity from the choice of the initial therapy, because now we're moving towards four-drug regimens.

But at time of relapse, there can be a lot of heterogeneity, and that reflects the variability in terms of what the relapse looks like. Is it something that's very gradual? When I think about a patient who's relapsing initially, I ask, what's the context? If a patient is on

lenalidomide maintenance, they're generally feeling pretty okay. They're back to their routine after dealing with all the drama of the initial diagnosis and their therapy.

Then, if they were to relapse, is it the doctor telling the patient or Stephanie, the nurse practitioner telling the patient, "Oh, you have this" versus the patient telling the doctor? They feel like something's going on.

Because the choice, in terms of the relapse therapy, you have to think about how to maximize the patient's quality of life.

Quality, as well as quantity, of life is important—living longer and living better. Some of the choices in the relapse therapy can be pretty intensive. Sometimes I wonder, if a patient has purely a biochemical relapse and is asymptomatic, do you really need to do a therapy that is really intensive and involved? Versus something that has similar benefit but might be more user friendly for the patient in terms of thinking about the quality-of-life part of it.

So, those are things I think about. That's why there can be a lot of variability. There are some patients where if it's purely just a biochemical, a gradual biochemical relapse, say they're 4 or 5 years out, and by then you've been on lenalidomide a long time.

Some patients do have loose stools and they have other problems that emerge with lenalidomide if they've been on it for a long time. Sometimes I use just daratumumab. But for patients where it's a more of a biochemical relapse, but I feel like maybe they should do something more than just daratumumab, I think about daratumumab, lenalidomide, and dexamethasone.

For patients who have more substance to the relapse or the patient has a clinical relapse—if, for example, a patient has a new bone lesion, like when John mentioned he has this rib issue, then he has this new soft tissue lesion—maybe you would reach for something that may have more efficacy. That's where I think about the carfilzomib option. Doing a CD38 antibody with carfilzomib may be more appropriate. But, you know, carfilzomib can be a little bit more work for the patient, because it's an infusion.

It may not be right for every patient. Again, you have to individualize that. Sometimes, if the patient doesn't have significant peripheral neuropathy, a proteasome inhibitor like bortezomib or Velcade, which they haven't had in a while, might be appropriate, too, to combine with a CD38 antibody.

There are patients where the treatment for their relapse lasts longer than the therapy they had for their initial relapse. That definitely happens. For that, you think about drugs that they haven't had before. Sometimes you think about using cyclophosphamide. Sometimes you think about using selinexor, which is approved for earlier lines, as well, sometimes in combination. Again, you have to think about what drugs people have had. Also, it depends on the timeframe when the patient was diagnosed.

John had thalidomide years ago, and you can see the pace of the drugs he's had.

And always think about clinical trials, as well. Because sometimes, you have to go to a center that could be hours away. That's something we have to think about. Is it worth the drive to do that?

For some patients, the clinical trial is the best way to treat. For earlier lines of relapse, relapses after one to three therapies, we think about these newer therapies that we're evaluating in early lines—CAR T therapy or bispecifics or antibody-drug conjugates.

Is it theoretically possible that CAR T therapy or something targeting BCMA could be even better than what the patient had in the very beginning? That's also exciting.

Mary DeRome (MMRF): Stephanie, what about patients who have comorbidities? Do comorbidities affect their treatment options?

Stephanie Sanford, MS: Andrew did a great job outlining, from the disease perspective, how we think about things and how complex that can be in itself. But then when you flip the coin and also think about, from the patient perspective, how they're presenting and their life outside of myeloma and how that might affect treatment decisions. It can be even more complex.

Diabetes in particular can be a problem. Dexamethasone is the backbone of almost all of our treatment regimens. As a steroid, it can increase glucose levels really out of control for patients and remove it from consideration as an option. Often we can work closely with endocrinology to get some numbers down and make the dexamethasone happen, but there are patients that just can't tolerate it.

Another thing with diabetes: some people come in with peripheral neuropathy or numbness or tingling in the fingers or toes. To try to add Velcade on top of that or add some of these regimens that we know might make already existing issues worse, people who come in with mobility issues or even obesity, that can make mobility tough, and we don't want to add peripheral neuropathy to that.

Kidney issues are also really common with myeloma and can be part of the disease process there. A lot of times we're able to manage that with reductions or switching out one treatment or one drug for another, but that can be something we have to monitor really closely and might, at some point, be something that excludes someone from a clinical trial.

Cardiac issues, especially with carfilzomib, are things that we have to monitor closely for things like high blood pressure and heart failure. One thing to think about, because people are living so long with this disease, is that these aren't issues that patients presented with 10 years ago. It might be that a different unrelated cancer develops in that time or an orthopedic problem develops in that time.

Sometimes something that you really didn't have to factor in earlier on, you get 5, 10 years out and it's almost a whole different health history now to make those treatment decisions. So, again, you just continue to build that individualized plan for the patient.

Mary DeRome (MMRF): Speaking of clinical trials, John, did you think about going on a clinical trial at any point through your disease course? What did your caregiver do at the time of your relapse that was really helpful?

John Selin: I didn't really consider clinical trials as long as there was a baseline treatment, the next treatment came along. Dr. Yee, by the third relapse, did show me

one of the clinical trials that he was working on. This was almost 4 years ago. But that's when we, decided to go with the dara triplet therapy. As Dr. Yee explained, it takes a lot more time. There's a lot more travel, tests and so forth. So that was it.

Certainly, my wife was my key support.

Mary DeRome (MMRF): Dr. Yee, should patients be asking about whether they're eligible for a clinical trial, even if they have an early relapse?

Andrew Yee, MD: It's always appropriate, because we do have clinical trials across all different stages of the disease process. It's always worth asking if a clinical trial is appropriate.

But as John mentioned, it's about individualizing to the patient's situation. In some cases, the clinical trial is the best option, but in other cases, the clinical trial can be a lot of work for patients.

Certainly, if John participated in a clinical trial, Stephanie wouldn't be part of his care anymore. John sees us in Danvers, which is great. It's close. It's super convenient for John in terms of minimizing travel, parking, etc.

A clinical trial does require more investment in time, energy, and more visits. I definitely appreciate that. But at the same time, clinical trials are great because definitely patients feel more empowered in their care and they're contributing to understanding the disease. They also have a of nurses and research coordinators that are dedicated to making sure that the trial goes as well as possible. It's almost like having a concierge service in a way.

But, again, I do appreciate that people go on vacations, maybe some patients spend the winters in Florida. The clinical trial does require that time commitment that you have to be in the area for the treatment.

Again, it really depends on where the patient is in their journey and what works for them. So, I definitely encourage patients to participate in trials when it works for them, because I'm really interested in trials, too, but I also realize it's two-way. We all have to work together. We want to make sure patients have a positive experience in whatever you're doing.

Mary DeRome (MMRF): We are almost at the top of the hour, so we're going to get some concluding thoughts from everyone. My final question for all of you is, what can patients or their caregivers do to prepare for the inevitable relapse?
John, I'm going to let you answer first.

John Selin: I've always discussed these things with Dr. Yee and Stephanie. How long is this going to last? How long am I going to have a good response? What are the options?

Talk with a doctor about the options for the next round of treatment, that's the main thing, Have a good outlook. My responses have already been very good when we've had to change. I've been very fortunate.

Mary DeRome (MMRF): It's so important to have a really good relationship with the care team. That decisions are made in a collective manner and that everybody considers all of the options and does what is best for the patient.

Stephanie, what can you tell us about how to prepare for relapse?

Stephanie Sanford, MS: One of my biggest pieces of advice here is to keep coming to your appointments and keep those conversations going.

A lot of people feel that weight of the relapse on them. What do I report? What do I say? Just thinking about it.

When you're coming to your appointments routinely, we can take some of that weight off. It's our responsibility to be monitoring your labs and to be asking you what's going on. Then we can make those decisions together. It's important to have as much support as you can outside of us, as well.

Some people have a bigger support network than others, but hopefully we can even connect with psychology or counseling just even for managing and those coping skills. If we can do this together as a team, and maybe connect you outside of our team to more resources, I'm hoping that can be as helpful.

Mary DeRome (MMRF): Dr. Yee, you'll have the final word.

Andrew Yee, MD: I wish I could say patients would never relapse, but in reality, relapse is part of the nature of multiple myeloma. But at the end of the day, the overall message I want to convey is a positive message: while relapses can occur, the treatment options we have are just increasing, more effective, and better tolerated. When the relapse does occur, if it does occur, what's available could even be better than what you already were on before.

While relapses are part of the business, the options we have for treatment are getting better and better. Patient education is really key, so they feel comfortable thinking about the next steps ahead.

Mary DeRome (MMRF): One of the things that we try to emphasize is that communication between the patient and the care team is key. You guys are a great example of really knowing how to communicate and really working together for the benefit of the patient and making decisions together.