ADVANCING THE MANAGEMENT OF PLASMA CELL DYSCRASIAS

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MS. VISOVSKY Hello everyone. Welcome back. My name is Connie Visovsky. I am the Associate Professor at the University of South Florida, College of Nursing, where I'm also the Director of Diversity. Please remember, as we start this session, to silence your cell phones for our next lecture.

We're delighted to have our next speakers join us. Please welcome Dr. Rachid Baz from the Moffitt Cancer Center and Dr. Beth Faiman of the Cleveland Clinic, as they discuss the management of plasma cell dyscrasias. I also want to say, before I turn the lectern over to them, that at the end of this session, if you will kindly remain for about a minute or so, I have some important announcements and housekeeping for you. Thank you so much and enjoy the session.

MS. FAIMAN Thank you. Thank you, all of you, who decided to stay inside in South Florida, and listen to our discussion. It's my honor and privilege to be here and Dr. Baz, who I'm going to be calling Rachid because he said he can't be my friend if I call him Dr. Baz –

DR. BAZ That's right.

MS. FAIMAN – much longer. So, Rachid and I go back many, many years and I think it'll be a treat for you to hear him present with me. So, our topic is Advancing the Management of Plasma Cell Dyscrasias. Our learning objectives are listed on this slide and in the interest of time, I'm not going to go

into each of these. Primarily, we're going to focus on the difference in differential diagnoses of plasma cell disorders. Our financial disclosures are there as well.

Most of you in the audience are very well aware of the diagnosis of hematologic cancers and you've heard many presentations, but this is a nice slide that was adapted from Sandy Kurtin's slide, of course, because everything is adapted from Sandy Kurtin and the NIH. And it describes the healthy bone marrow and as that cell develops, it differentiates into the myeloid and lymphoid lineage. So, what you see is the lymphoid side is where we see most of our plasma cell disorders. So, in many patients with an abnormal protein, we will look for a monoclonal gammopathy of unknown significance, systemic AL amyloidosis, and multiple myeloma. And then we have, in this pie chart, again this is the distribution of monoclonal gammopathies from Dr. Robert Kyle, this was published years ago in 2004 and needs to be updated, but we do find a lot of patients with this monoclonal gammopathy who secrete an abnormal paraprotein, and most of those individuals never go on to needing treatment or requiring treatment. As you can see here, about 15% in that pie chart have myeloma and about 10% an amyloidosis.

So, multiple myeloma, as you are very well aware of, is a cancer of the bone marrow plasma cells that is often preceded by the asymptomatic MGUS or smoldering myelomas, and the healthy plasma cells will produce antibodies or gamma globulins, but there's that overproduction of one clone of a normal protein that requires the good baseline workup and good monitoring. Dr. Baz, what kind of test do you use at baseline to diagnosis monoclonal gammopathies? I have

listed on this slide, a few things here. Is there anything listed that you would think needs to be on this slide?

DR. BAZ You know, I think these are, you know, very good starting tests. I do check for amyloidosis as a screening tool so I do obtain an NT-proBNP and troponin for all patients who come to my clinic to eventually, essentially associate with amyloidosis. About 10% of patients with myeloma will have amyloidosis, as well, and so if we don't think about it, we don't make that diagnosis.

MS. FAIMAN Yeah. Absolutely. And we're going to talk about the testing a little bit more in detail in a moment, but I'd like to think of the plasma cell disorders within case studies. So, this is a 51-year-old accountant and an avid runner who presents to the APP clinic with significant back pain. Because they always seek us APPs out before their doctors, in many cases. The complete blood count showed a little leukopenia, mild anemia, mild thrombocytopenia. The creatinine was elevated, which was odd because historically he had a normal creatinine. Calcium 10.4. His serum total protein was 10.9 gr/dL. So, on the previous slide I had listed tests like SPEP, UPEP, free light chains, and this is a nice slide to take with you. And, again, you'll have access to all of these slides and on the left of this, you can see the test that's recommended per the International Myeloma Working Group Guidelines, and the possible findings with myeloma. And as Dr. Baz had mentioned a moment ago – Rachid – that he does screen just about all of his patients with renal insufficiency and a paraprotein for

amyloidosis by adding an NT-proBNP, and we'll learn why later on in our amyloidosis portion.

This serum protein electrophoresis you can see in the top corner of the slide, is a graphic that shows the majority of the immunoglobulins will migrate to the gamma region. If your patient has an IgA type, that will migrate to the beta region, however. So, in terms of his additional labs, there was an elevated IgG and kappa, which were quite elevated, 24-hour urine was normal though, which kind of rules out a little bit amyloidosis. Anemia showed a low B12, high methylmalonic acid, suggestive of B12 deficiency, and I had cited a paper that Dr. Baz did, when he was in his residency with the –

DR. BAZ That was one of my first papers –

MS. FAIMAN – the first paper in association of vitamin B12 deficiency in myeloma and, what is his diagnosis, Bob? You can tell us.

DR. BAZ Well, before we tell you, I'm going to talk a little bit about the pathophysiology of myeloma. And I think a lot of patients present today a bit differently than they did years ago. I think a lot of patients could be asymptomatic today. If you think about ways that patients could present, there could be signs of marrow infiltration and we typically think about anemia and cytopenia, but you know, also there is bone destruction that could occur and that can result in fractures, bone pain, hypercalcemia. Patients who have myeloma also may have hypogammaglobulinemia, which results in opportunistic infections and some form of immune deficiency. The monoclonal protein itself serves as a tumor marker, and a lot of times, innately used as a tumor marker to track the

disease and, that we'll go over response criteria later on, but itself, it can also cause renal insufficiency, as well with the light chain deposition or cast nephropathy. And some patients have also neuropathy as a result of either amyloidosis or deposition of the monoclonal protein in the nerve endings.

If you think about the differential diagnosis of plasma cell disorders, we've been using this slide for a while and there's been some recent changes over the past few years. But if you think about patients who have MGUS, these usually have less than 10% marrow involvement, a small monoclonal protein, typically less than 3 grams, but very frequently, less a gram-and-a-half, and they have no myeloma defining events. The prior terminology we frequently used was CRAB criteria. And we go over this CRAB versus myeloma-defining event, but in essence they should not have damage to the body that’s either present or eminent that's due to the plasma cell disorder, and those patients have a likelihood of progressing to myeloma of about 1% per year.

Patients in the middle category have smoldering myeloma of over 10% marrow involvement. Recently, there's been an upper limit cutoff of 60%, recognizing that patients who have more than 60% marrow involvement almost always will develop symptomatic disease that requires treatment, and those patients also don't have any myeloma-defining event or damage to the body. And they have a higher likelihood of progression to myeloma in the first 5 years, but subsequently, it's a reduced likelihood similar to MGUS. And currently for MGUS and smoldering myeloma, the standard is to observe, and there are some debate

on whether clinical trials will be more appropriate for maybe the high-risk smoldering patients.

Active myeloma is defined as over 10% marrow involvement of monoclonal gammopathy with evidence of myeloma-defining event of CRAB. So what are those? CRAB, hypercalcemia, renal failure, anemia, and bone disease. And that's where perhaps myeloma is different from any other condition in oncology where oftentimes if you have a patient who has a breast biopsy showing breast cancer, everybody agrees, this is breast cancer. But in the case of –

MS. FAIMAN Not in myeloma.

DR. BAZ – myeloma, the diagnosis is a clinical pathological one. Meaning that you have to put the clinical features, the lab features, the imaging features, along with the pathologic features to make the diagnosis. And some patients for example, could be 80 years of age and have a small monoclonal protein, some renal insufficiency and that doesn't make it myeloma. So, those are patients who don't require treatment.

On your right, there is this myeloma-defining event. This is what was added a number of years ago now, 3, 4 years ago, recognizing that some smoldering myeloma patients have a higher likelihood of progression. And depending on which criteria you use, some of them have about 80%, a 2-year likelihood of progression and perhaps those patients should be considered for early treatment rather than wait until damage to the body has occurred. I think for a lot of those criteria, it's reasonable, but my plea in terms of understanding those

criteria, and I'd love to hear from what they do in Cleveland, what's best, is that those criteria are not equal. Philosophically, bone disease is bone disease, no matter how you define it and diagnosis it. On the other hand, an abnormal free light chain ratio, it's a little bit, but there's a higher likelihood of progression, that likelihood isn't 100%. Are we justified in starting treatment immediately? And what those criteria do is they allow you to treat the patient who you're concerned about. But they don't obligate you to treat patients immediately and, it's very reasonable to watch. What do you think best?

MS. FAIMAN I have several patients with a kappa light chain ratio that are over 100 that I've been watching since 2004. Some of them were your old patients, Rachid, and just not everybody requires treatment, but these criteria were set forth based on, by analyses that suggested that the likelihood of needing treatment in 2 years was there, and so this was to not to wait for the myeloma-defining events, or the CRAB. It was to give you the approval to start early if you felt that it was clinically necessary.

DR. BAZ So, yeah, absolutely. These are patients I could monitor very closely and, you know, if their paraprotein and tumor marker is rising, then I won't have to wait for a CRAB criteria but rather initiate treatment –

MS. FAIMAN Correct.

DR. BAZ – perhaps. So, going back to Bob, actually quickly. So, it was felt that Bob had smoldering myeloma because none of the organ dysfunction that were noted were felt related to his disease, and that's where there's a little bit of subjectivity to the myeloma diagnosis that doesn't exist in any

cancer, other cancers certainly. And, you know, you're going to need to enroll in trial, you know, for high-risk smoldering myeloma.

Now, smoldering myeloma, we talked a little about this as the middle entity where, you know, patients don't have the disease quite in terms of organ dysfunction, but they have the tumor burden, so to speak.

MS. FAIMAN Mm-hmm.

DR. BAZ And perhaps one of the ways to look at this, I think the simplistic way that I would have towards this is that I don't think smoldering myeloma really exists. I think smoldering myeloma represents two distinct groups of patients; one that already has active disease but biologically – but we can't find it yet, causing organ damage, but it's going to happen. And then there's the other group of patients who really have MGUS, and the same biology there. So, nevertheless, that's why it's very challenging to look at this as a uniform rule.

MS. FAIMAN Mm-hmm.

DR. BAZ And that's why a trial like this where patients receive aggressive treatment with carfilzomib, lenalidomide, dexamethasone, transplant, more consolidation with the induction drugs, and even though the results are outstanding, one has to ask the question, what is the cost of these results and how durable are – what are the long-term data going to look like? And this is a work in progress, I would say.

MS. FAIMAN Absolutely.

DR. BAZ Another approach is the single-agent that our tumor map study presented at ASH, and they had three arms, so there was an

intensive arm where patients continued on treatment. And there was a short intensive arm where the patient only got the subset of treatment, but didn't continue. And if you can look at the curves, you basically could tell that patients who received intensive treatment and stayed on it for the longest time, did the best.

MS. FAIMAN Mm-hmm.

DR. BAZ Ultimately saying that we're not curing those patients if we don't continue the treatment, so meaning that there was no cure in sight here, but it may be helping delayed progression. Would that be –

MS. FAIMAN Absolutely, and I think that Dr. Baz just showed you, intensive transplant in smoldering versus these people that just got a little bit of a single-agent monoclonal – I was going to say monoclonal protein –

DR. BAZ Antibody.

MS. FAIMAN Monoclonal antibody. Thank you for being here, or else you'd be stuck with just me. But so it's great data but at what the cost? So, that's interesting.

DR. BAZ So, you know, when you look at the pros and cons of early treatment for smoldering myeloma, there's one study that showed a survival benefit. This study had a lot of pitfalls and I think it's a small study. Certainly, compelling, interesting, thought provoking, but I think this is one of those things that's possible survival benefit. We may be able to delay progression. That's certainly a good thing too. And, potentially contemporary treatment, beyond that study, could be even better. The study used lenalidomide-dex, but there could be

a more intensive treatment that doesn't have to be associated with a lot of side effects.

On the downside, not all patients are going to need treatment. If you just do the math and follow the statistics, not everybody needs treatment. And if you treated somebody and gave an unnecessary treatment, unnecessary side effect, well, that's over-treatment and there's implications for concerns for long-term toxicity, other malignancies, in fact, in terms of quality of life, financial impact. So these are some of the reasons why the standard of care for smoldering myeloma remains to watch or to consider a clinical trial.

MS. FAIMAN Yes.

DR. BAZ Is a cure possible for myeloma? I think that never before have we had as many agents as we do today to treat the disease or as many modalities and the risk keeps increasing. And we've gone beyond looking at response just with immunofixation and serum protein electrophoresis, and we can look at minimal residual disease, trying to detect basically what's the lowest level of myeloma in the body around one cell in a million in the bone marrow, so this is awesome and never before could we even envision doing this.

On the other hand, there are still pitfalls to doing this and we still recognize that the disease is largely incurable. And so while detecting and following minimal residual disease is proving to be a very useful tool for clinical trials to assess whether two different treatments and how comparable are they as part of clinical care, this is difficult to adopt yet in terms of how do you change your practice? There are tests that are available. This is data presented by the IFM

that show that patients who are MRD negative at 10^{-6} have better outcome, may not need a transplant, for example.

MS. FAIMAN Mm-hmm. Right.

DR. BAZ And even if they have high-risk disease, they may not need subsequent treatment. But how do we take this a step beyond? So, we're starting to test for this, but not yet very much in terms of how does it affect decision making? Have you started checking for MRD?

MS. FAIMAN No, we're trying to get the assay, the –

DR. BAZ The Genoptix?

MS. FAIMAN – yes, in our clinics and so it's a challenge. It is commercially available and there is reimbursement from the company and so that is something that we're moving forward to in 2019; hopefully, we'll have that. It's nice to know information outside of the clinical trial, but not need to know. If I have a CR for 11 years, on lenalidomide maintenance, that doesn't mean I would take them off of treatment. I don't have that information yet. But it's nice to know we all have that option.

DR. BAZ I think it's key in terms of looking at MRD, trying to figure it out. There's a different testing modality, there is flow, there is sequencing, and currently the commercial test is Genoptix sequencing-based, and Medicare does pay for it. So, it's something that we're starting to look more at, but – exactly – we don't know how to tie it yet, in terms of decision making.

MS. FAIMAN Exactly. So, undergoing screening for this high-dose CENTAURUS trial that Bob wanted to participate in, he developed back pain and

a fracture when lifting furniture. So, as you can see here, these are some commonly progressive skeletal fractures. You can see the osteopenia in the plain film skeletal survey. You can't see very well the vertebral bodies. In the middle, you see the osteolytic lesions that are occupying that vertebral body and then onto the very far – is it the right or your left? The very far right, is that T6 wedge deformity on MR with an altered marrow signal. So, unfortunately Bob didn't get to go on his clinical trial and so now, we have to decide what do we give him? And I think of things in buckets. So, in general, in the United States, in 2018, we do an induction in situ, reduce with four to six cycles of A, B, or C treatment. The standard of care in the United States—we'll hear from Dr. Baz, some data—but it tends to be a triplet combination. Consolidation with high-dose melphalan in the form of an autologous stem cell transplant. That's debatable. We saw some data that MRD negativity can be achieved by just a good induction and maintenance, but that is something that we offer to patients in many cases. Maintenance to maintain that response and then relapse rescue. So, the treatment decision making needs to be made and this is a list of our cornucopia or our buffet of options. There's so many drugs. And in 1996, when I started doing myeloma, there were alkylating agents and transplant, which is kind of the same thing because it was cyclophosphamide and melphalan. We had some bad, but for those of you that have been in the game for a long time, you can see, we have classes of drugs now. We're like other cancers. We have the IMiDs, which are oral, proteasome inhibitors, anthracyclines, alkylating agents, steroids, etc. So, for those of you, we'll go over some of these drugs, but bortezomib len-dex is a

standard of care. I'm not going to go into great detail. These next two slides have side effects of common drugs. The idea here is when you're mixing and matching drug classes, typically an IMiD, proteasome inhibitors, and corticosteroid, you don't want overlapping toxicities. And it's nice to be – and again, when you start a treatment on your patients, really research the common side effects and think about whether or not there are overlapping toxicities. Rachid?

DR. BAZ So, I practice in Florida. And right around Tampa, there is Sarasota; it's a much older community, I would say, and treating myeloma is more of a challenge when patients are older. I think the two settings where there is really an unmet need now for myeloma is patients who have high-risk disease, but also patients who are elderly. And a lot of the studies have defined elderly as 65 and over, but that's a young patient in my clinic.

MS. FAIMAN Mm-hmm.

DR. BAZ And I think we have to look at age as a continuum. There's a lot of work that has been done by the Italian group looking at frailty and geriatric assessment for patients with multiple myeloma. There are many different ways to do a geriatric assessment. The Florida way, by the way, is 18 holes of golf, is a good patient. It's fit. Nine holes of golf is an unfit patient, but no golf is actually a very frail patient. So, where there's that, where there's also the formal assessment. There's a link that you can follow. And basically, if you look at patients who are over 80, by definition, that being the frail category. Patients over 75 with a comorbidity, that is meaningful, then that would be in the frail category as well. Now, I think the key setting what to look for frailty is that

patients who are between 70 and 75, where the patient might be frail and you're not sure. Say, they have two risk factors in that setting, that fall in the frail category, frailty tends to predict outcome in myeloma much more powerfully than cytogenetics, I assess stage, and it's something that we have to be very mindful when we're approaching patients who are frail. And obviously, you know, older patients can come in many different flavors. Some old patients may not be frail, so we have to be mindful of that.

This work study compared induction regimens and also it was meant as a trial that didn't have transplant as part of it. Patients were eligible for transplant, they could participate as long as they didn't want to have do an immediate transplant. And randomize patients to VRD, bortezomib, len-dex versus len-dex. And basically, six cycles or 6 months of VRD, six cycles of len-dex and then patients stayed on len-dex maintenance. And the 6 months of additional bortezomib increased the PFS by about a year and it increased median survival by about a year, which is remarkable. You give a drug for 6 months, you have a year increase in median survival. That came at a cost. The cost was neuropathy, GI toxicity, and we realize now there may be better ways to give bortezomib than what was done in that study, it was intravenous bortezomib, but nonetheless the study is very compelling and that's what pushed VRD to be the standard of care in myeloma for newly diagnosed patients today.

The IFM study was to answer the early versus late transplant and basically patients got VRD induction, collection of stem cells. They either proceeded to transplant or did not. If they did not, they got a little bit more VRD. If

they did proceed to transplant, they got a little bit less VRD than what they would have in the other arm and everybody went on maintenance with lenalidomide.

And basically, if you look at the median progression-free survival, was better in the transplant arm, but the 4-year survival has been identical with both arms, suggesting that if you're looking at biologic effect, doing the transplant early gives that benefit; however, you know, for patients who might defer the transplant for later on, they would not, you know, lose in terms of survival benefit and that could still be meaningful and feasible.

MS. FAIMAN Mm-hmm.

DR. BAZ Maintenance therapy is very important. I think when you think about a cancer you don't cure, you have to keep the pressure on the disease. The standard of care for maintenance after transplant is lenalidomide. It's the only approved drug for that indication, but it doesn't mean that's the only agent that is used and there's other agents that have been studied and there are studies of combining elotuzumab to lenalidomide, ixazomib maintenance has been studied, ixazomib and lenalidomide maintenance has been studied, and there are some post-maintenance consolidation of treatments that could be also considered. In the interest of time, we're going to be a little bit on the short end of this, but you know, if we have questions later on, please approach either one of us and we'll go over this as well.

We have to think about myeloma not as one disease, as multiple diseases. It's multiple clones within the same patient and this is a very elegant study that was done by the Mayo group where a patient diagnosis had about five

or six clones, and that's shown in that mostly pie chart that's mostly red. And he received lenalidomide-based treatment. There was a little bit of a decrease in that red clone, but an increase in the orange clone. But with subsequent treatment and progression, there's the emergence of a clone that was a minority of the clone and ultimately, throughout the treatment history, the patient dies from a clone that only represented a minute fraction –

MS. FAIMAN Teeny tiny amount.

DR. BAZ – of the original makeup of the clone.

MS. FAIMAN It was so strong, that line of clone, that it evolved over years of therapy to be like a blue martian –

DR. BAZ So, whenever you think about myeloma, you have to think about in those terms. There are some patients who don't have this clonal evolution and have more of this hyperdiploid, steady clones, but these are usually the low-risk patients. High-risk patients are more likely to be have a behavior like this and that has challenges. We don't do this routinely on patients, this kind of testing, but it may be something that in the future may be coming.

MS. FAIMAN Absolutely. So, it bears mentioning, so Bob went on the study. He had a zero after transplant. He achieved a complete remission and then his M protein started slowly climbing up, signaling a biochemical disease progression, so that bears watching. You know, how often do we monitor patients after initial therapy? Well, we can expect most patients to get 3 to 5 years of leverage out of whatever treatment you give. Here on this slide, highlights the International Myeloma Working Group criteria, and I won't go into great detail. I

do want to highlight that the PR is a 50% reduction in the paraprotein from diagnosis. CR is when you have no evidence of a paraprotein in the serum or urine and then now, in that little circle, are some of the newer types that are within clinical trials, primarily. With that, looking for one out of a million cells with that MRD status. The idea is that you look at the diagnosis, what do they present with? Do they have IgG kappa myeloma? You look at the SPEP. They have light chain type, lots in the urine? You look at the blood and the urine as well. And so just keeping an eye on the myeloma disease characteristics is very important.

DR. BAZ One more thing – this can be confusing. It's not. Don't worry about it. A lower M protein is –

MS. FAIMAN The better.

DR. BAZ – a good thing. But the key thing is that if you're following for a patient on a clinical trial, you have to go in those details.

MS. FAIMAN Mm-hmm.

DR. BAZ For a patient outside the setting of a trial, where there's – we call it a VGPR or an nCR and those kind of minutiae may not make a big difference to the management.

MS. FAIMAN I agree. I don't get caught up in – how do you know if your patient is responding, if the protein is going down. If it gets up, that's bad. And some people will like to deepen response by adding agents but that's not necessarily necessary, currently, outside of a clinical trial. But this is a list of, you know, we have all these FDA-approved drugs, at first relapse. And so that's where you bring in what's the data and experience? How deep can you get a

response rate with using three drugs versus two versus four? What's your patient preference? So, these are concepts of shared decision making, so you as an advanced practice provider can have that important role in conversing with your patients. Maybe they want to go to Florida and play golf, and I send patients to Rachid all the time in the winter months. Maybe they want to take an all-oral regimen so they can travel, and so balancing those things are very important.

In selecting the next treatment, at relapse, in somebody like Bob, you know, he's a young, healthy guy, he wants to be active and around for his family. You take into consideration the disease related factors, such as the cytogenetics and the FISH analysis. Do they have high-risk clones? You want to see, was it a slow biochemical relapse or was it aggressive relapse? We want to think about treatment factors. Does the individual have peripheral neuropathy from bortezomib or other agents? Do they have diabetes? You want to mindful of the steroids and cost and mode of administration. Dr. Rachid, what kind of therapies do you think of in relapse?

DR. BAZ I think there is not one way to approach relapse, and that's where maybe medicine becomes more art form than science.

MS. FAIMAN Mm-hmm.

DR. BAZ And then we have to have a discussion with your patients about the goals of care, what's important for them, what do they really like to do? I don't think, you know, you have to look at it first. Do I really need to treat the patient? Not every relapse requires treatment. I have a couple of slides here that goes a little bit into my approach. I'm going to skip those next few.

But it is basically losing those criteria that are disease-related, patient-related, regimen-related, some of the patient preference features. But I would look at it into two broad categories overall. There's the indolent patient, which is the indolent relapse patient who typically first relapse, patient on maintenance. The numbers of the M spike, as you can see are slowly rising and it may have taken, maybe a year for the numbers to double in numbers. The patient usually has low-risk disease and maybe you can try to make a small manipulation to the treatment. Not change everything dramatically and still gain more mileage out of your treatment.

MS. FAIMAN Sometimes if they are on one maintenance, we just add back steroids. So, if they had a transplant and it's a slow relapse, we'll add steroids, or ixazomib or an oral –

DR. BAZ Absolutely –

MS. FAIMAN – proteasome inhibitor.

DR. BAZ – we have a trial for that setting, for example, at Moffitt, where we're adding elotuzumab to lenalidomide when they have progression. And so see there are minor maneuvers where it's not going to impact quality of life, not causing too many symptoms. On the other hand, for patients who have aggressive relapse, this is a patient who has, what we call, free light chain escape, or light chain escape, didn't have high light chains at diagnosis, that you can see. His M spike actually remains low, but his light chains go up really rapidly, usually with symptoms. And in those cases, you have to give aggressive combination treatments to try to control the disease.

MS. FAIMAN Carfilzomib is good for that, and to say, aggressive relapse, we do a lot of carfilzomib as well.

DR. BAZ Absolutely. And things that you can keep in mind is that – think about it this way. The disease-related symptoms have to always be – we have to always carefully manage those, so the treatment-related side effects – if your side effects are more than the disease symptoms, then you're not doing something right at that point.

MS. FAIMAN Yeah.

DR. BAZ And there are some pitfalls too to our approach. Obviously there are newer regimens that have multi-agent treatments, but they're not necessarily having overlapping toxicity and it may have less symptom-related problems and maybe better quality of life by getting, for example, KRd versus Rd whereas even though it's a triplet. So, that's a testament to the fact that a lot of our treatment today is better tolerated.

There's a lot of options for relapsed/refractory myeloma. These are the regimens that have been studied using those six drugs that we have been approved for the past 6 years and we're not going to go over them, but you know there's a lot of choices and how do you pick, and we try to find medicines that the patient hasn't been exposed to, that their likely to tolerate well, and in early relapse we can try to be a little bit picky in terms of convenience and preference, but in late relapse, maybe are more limited.

MS. FAIMAN I have a question for you, Rachid. So, we have this idea. Are you lenalidomide refractory, or bortezomib refractory? So, if somebody

started on lenalidomide maintenance and then they're progressing, at what point do you stop just adding things and switch around?

DR. BAZ Yeah. Nobody really knows, to be honest. If actually adding things or switching around is the best way to approach things from the get-go, to be honest. If you look at patients who likely have clonal evolution, perhaps one can consider that maybe piling on drugs makes more sense, but the opposite can be made. You know, the opposite argument can be made. I think if you think about doing in a lenalidomide-refractory patient and want to give pomalidomide-dex, the response rate is 30%.

MS. FAIMAN Mm-hmm.

DR. BAZ So, there is activity. If you have a bortezomib-refractory patient and you want to use carfilzomib, the response rate is probably in that 20% range. And then by combining agents, you're not going to have a higher response rate, and I think these are some of those things that you have to weigh in terms of likelihood of benefits, but also likelihood of toxicity.

MS. FAIMAN Thank you. So, I just wanted to run through a couple of the drugs that we've highlighted and skipped over all those big slides. So, carfilzomib is a proteasome inhibitor. It has these three indications that are listed on this slide and I'm so thrilled that we have different classes of drugs, but it makes a 50-minute presentation a little burdensome, right? There's just so many drugs to go over. I think most of you are aware, since it's approval, and it's a single agent in 2012, which is not on this slide, the clinical pearls. We do just have an approval of 70 mg/m^2, which we'll talk about in the ARROW trial in a few

moments, but the overall survival with a triplet drug with KRd, versus the people that just got two pills Rd, which was a tremendous overall survival benefit. Patients should be maintained on herpes zoster virus protection. And in my opinion I think all patients these days, because whether it's a monoclonal antibody or a proteasome inhibitor, or they've had transplant in the past, shingles can be a big issue. Rachid, what's your thought on the shingles vaccine?

DR. BAZ So, I think it's going to be a good addition. What we really don't know yet is, is it going to be enough to prevent VZV or shingles in patients who are taking, say, bortezomib or carfilzomib? We do know it's effective and safe for the myeloma patient population but we haven't really studied it in combination with those agents or the monoclonal antibody. The other thing is that, I don't know about you guys in Ohio, in Florida there's a shortage.

MS. FAIMAN Yes, there's a nationwide shortage. So my patients are emailing me, "Can I get this vaccine?" I said, if you can find it and find somebody to pay for it, yes. But otherwise, we're not sure we have it. The ARROW study was a randomized study of carfilzomib-dex with once weekly added dose of 70 mg/m^2, over 30 minutes versus twice weekly 20/27 which is our standard dosing. Again, the aim of this study was to see if a higher weekly dose, so that you're not burdened by going back and forth to the clinic, was just as safe and effective as the other dose. And, you can see here the progression-free survival on this slide of patients with the yellow had the KB once weekly, did just as well, as the patients, actually better than – a little bit better, but, it was a noninferiority trial if I'm not mistaken, than the twice weekly. I'll just do another

point on that study, we're really worried about cardiac and it didn't seem to be that there were any more safety signals in terms of cardiac toxicity in patients with the higher weekly dose versus the twice weekly dose. Rachid, do you have any experience with that higher dose?

DR. BAZ I like the weekly schedule. I think the patients like it too because it's less visits to the center. We haven't seen any more toxicity. I've switched a lot of the patients to the weekly schedule because of convenience. And there are weekly combination with lenalidomide that you could use. There's an ASCO abstract we had that study open at Moffitt and I think it was very easy to give regimen in terms of the convenience. With carfilzomib, oncologists are not very good at managing hypertension. I usually told patients, “Well, you know your blood pressure is high because you're at the cancer center. But you have to be mindful for hypertension with carfilzomib. If you don't manage this aggressively, you could get, AFib, or other issues.” Cardiac toxicity is real, but it's infrequent in terms of severe events.

MS. FAIMAN Yes, absolutely. Pomalidomide is FDA approved in combination with carfilzomib, daratumumab, and by itself. And, Rachid, you were the lead author on a publication or two on the pom-dex versus dexamethasone study. Basically as an oral IMiD, it can be given with just about everything we have available. The main considerations are risk of DVT in patients who are receiving IMiDs and actually high-dose carfilzomib, the ENDEAVOR trial showed an increased risk of thrombosis. So, risk stratify your patients. So, if they're not moving around, that stasis is placing them at risk. Most of you are probably

aware of the aspirin that most people should be taking once a day. Although if they had prior DVT or recent surgery, cardiac or renal disease, then anticoagulation should be recommended. Encourage patients to stay well-hydrated and of course the REMS is in place with all IMiDs. Ixazomib is an oral proteasome inhibitor. It's FDA approved and indicated for relapsed myeloma in combination with lenalidomide. Again, as an all oral therapy which is very attractive to most patients. It's three pills a month, has a long half-life of about nine days and it is absorbed quite quickly. So, if patients are sick after they take it, then you don't have to readminister it. In the patients, 722 patients in the large study, there was an improved progression-free survival. So, we are talking about that slow biochemical progression, oftentimes for patients on just single-agent lenalidomide, we'll add dexamethasone and ixazomib. Another reasonable addition would be elotuzumab. Elo-len-dex is FDA approved in 2015 and there was a clear advantage and progression-free survival when patients took elotuzumab versus Rev-dex and the – don't look at the graph. That's not the right Kaplan-Meier curve, that's Kd versus Vd.

DR. BAZ Yeah. Good point.

MS. FAIMAN Out of all these iterations, I've looked at these slides like a million times, somebody just took a picture of that. Uh-oh. It's out there forever. That's by the way, the ENDEAVOR study, which studied carfilzomib-dex versus bortezomib-dex and Kd was superior. Just for clarity though, but the elotuzumab is – what a way to find out you did something wrong when you're making slides. But elotuzumab is a monoclonal antibody targeted against

SLAMF7 signaling lymphocyte family activating Factor VII. And it's generally well tolerated. Daratumumab is our second monoclonal antibody that is FDA approved in numerous indications. There are a few listed on this slide. And again, with monoclonal antibodies we want to be mindful of the risk of infusion reaction. Daratumumab carries an interference risk with the type and cross-matching and interference with complete response, which elotuzumab does as well. So, when your patients have IgG kappa myeloma, they might not look like they're in an excellent remission, but as long as the paraproteins coming down, anyhow, they should be in good form.

Bone-modifying agents, as we know, CRAB is part of the criteria of bone. And so, there is recent ASCO guidelines from January of this year, Ken Anderson is the lead author on that. And it's basically recommended everybody with myeloma should be treated with a bone-modifying agent. For you older folks in the audience, we used to just call them bisphosphonates. Now, because denosumab is FDA approved, then these patients, which is a RANK ligand, and it can be given monthly subq for 12 months. That can help prevent bone loss. It's really important to make sure those patients are on calcium and vitamin D because hypocalcemia can be quite profound. That is safe in renal disease as well. But denosumab – but whereas pamidronate and zoledronic acid are contraindicated with GFR, less than 30 – Rachid, what's your experience, before we move onto amyloid, with bone disease? How do you – what's your practice? How long do they stay on bone-modifying agents and what do they get?

DR. BAZ So, patients who have bone disease at diagnosis, usually will get monthly therapy with either zoledronic acid, or denosumab, zoledronic acid or denosumab. I usually give zoledronic acid for patients who have normal renal function, denosumab for patients who have abnormal renal function. You could argue to give denosumab for everybody. I think it's just more expensive and, quite a bit more, so I haven't gotten to figure out if it makes sense to justify the cost right now. And in terms of patients who don't have bone disease at diagnosis, they'll still get the bisphosphonate or denosumab, however, it be every 3 months. When patients are in a good response, they will be going to a less frequent schedule, typically for patients in CR after transplant, maybe it could go to once every 3 or 6 months, or even once a year if they've been in CR for a very long time. Discontinuation could be discussed as well.

MS. FAIMAN Mm-hmm.

DR. BAZ But I think there are still a lot of unknowns, or unanswered questions in that setting. And patients always ask us, but you ask 10 myeloma docs the same questions, you'll get 10 different answers.

MS. FAIMAN Twenty answers, because they change their mind.

DR. BAZ We do change our minds.

MS. FAIMAN Tell us about amyloidosis.

DR. BAZ All right. Amyloidosis, so you know, I tell patients amyloidosis is not one condition, it's multiple different conditions. And the one that hematologists get involved with is AL amyloidosis, or immunoglobulin amyloidosis, and oftentimes they have light chain. Occasionally, AH amyloid

occurs, heavy chain amyloids, still managed by a hematologist. Every other amyloid is typically not managed by a hematologist –

MS. FAIMAN Any one.

DR. BAZ – however, it's important for hematologists, or APPs to recognize that actually it did exist and that it doesn't require management by a hematologist, so that's where I think there's the differences. But amyloid refers to protein deposition. And where the protein comes from and what protein it is, actually is what kind of amyloid it is. If it's immunoglobulin light chains, then it's AL amyloidosis. I tell patients it's kind of like egg white and egg whites freely flows, but –

MS. FAIMAN Mohammed told us that. As you know, Mohammed Hussein.

DR. BAZ Yeah, Mohammed, exactly. So I use it and I think that they understand, and then they ask me if they can eat egg whites or –

MS. FAIMAN Should I avoid egg whites now? Because it's like an egg white hardens and it hardens your – yeah.

DR. BAZ But you know the goal here is basically to make the diagnosis quickly. Because we don't have any treatment that removes the amyloids from the tissue. There was some hope recently that was all dashed in April of this year, when one of the compounds that we were hoping was going to do that, turns out that you know the phase 3 study showed it doesn't have that activity that we were hoping it might. So, AL amyloid we talked about. AA amyloid is the patient who has rheumatoid arthritis for many years and has amyloid

deposits. That's the typical story that you won't have to elicit very hard. They'll tell you. Well, I've had RA for 20 years. It's not one of those undiagnosed already. Other types of amyloidosis exists and this is wild-type transthyretin but there is heredity transthyretin where patients typically could be even younger and they have family history because it's autosomal dominant.

I think about amyloid this way. There are cells in the bone marrow, you see them on the top left corner, and they are producing this immunoglobulin that's, you know, defective. And that immunoglobulin is depositing in the tissue either in the form of amyloid or light chain deposition disease. Slightly different condition, but as far as the hematologist is concerned, very similar management. We attack the plasma cells. What makes the protein in the first place. The goal is to suppress the protein and hopefully that can stop the damage. And, hopefully, with time, organs will improve. Now, you know, we think about it in those terms that there's ways to make the diagnosis and Congo-red positivity is typically what you hear on board type questions. And, there are other stains, thioflavin is particularly used –

MS. FAIMAN For the heart.

DR. BAZ – when you're looking at the heart, but in reality, the key thing to diagnosing amyloidosis is suspicion of amyloidosis. You will not diagnose this condition if you do not think about it. Very simple. So, you know, and if you're waiting for patients to present with a very large tongue, or a geographic tongue or –

MS. FAIMAN I never see this in my clinic anymore, but I put that on the sign because it's –

DR. BAZ Neither do I. Or the racoon eyes. Then, you know, that's going to be very late presentations. The earlier presentations are these. That's when you need to have an index of suspicion. A patient who doesn't have diabetes and has nephrotic syndrome, in my book, has amyloidosis until proven otherwise.

MS. FAIMAN Yep.

DR. BAZ A patient who has nonischemic restrictive cardiomyopathy with monoclonal proteins, think amyloidosis. Not diabetic neuropathy. A patient who has myeloma but is not responding to treatment in the right way, having unusual toxicity, spending a lot of time in the hospital with heart failure, through effusion, think amyloid. If you're waiting for macroglossia and raccoon eyes, this is going to be late presentations. So, the key thing is early diagnosis, consider screening patients with plasma cell dycrasia because 10% of those patients will have amyloid at some point. And so if you have a 24-hour urine, which has a lot of albumin in it, but very little of the light chains, the light should come up, amyloid.

MS. FAIMAN Mm-hmm.

DR. BAZ NT-proBNP troponin – we talked a little bit about it. Patients who have an echocardiogram showing a large septum, an EKG with a low voltage, these are things that, you know, should already clue you in. The pathologist will stain for amyloid if they see evidence on H&E of protein deposits

around blood vessels, but if you have a suspicion, ask them to do it on the bone marrow. The bone marrow yield is like flipping a coin, 50/50. The fat pad increases that yield to about 70-80% and it's an easy procedure to do. The gold standard for the diagnosis is amyloid piping, which is done by laser microdissection and mass spect. Only one place does it commercially currently, is Mayo Clinic, so. And VU also does it, but not commercially; they will do it for their own patients there.

MS. FAIMAN Mm-hmm.

DR. BAZ Suggested testing, we talked a little bit about the fact that EKG show low voltage, echo will show this, you know, sparkling appearance of the myocardium so if you have those both questioned, sparkling appearance, low voltage, interventricular septum. The only reason why anybody would measure the septum in a board question is for amyloidosis. I really don't think there's other people who look at the septum other than myeloma and amyloid docs.

MRI is very good at diagnosing amyloid. It's a very sensitive test, but it's in the right hands, it's also operator dependent. You need to have a person who can interpret it. Obviously, you know, endomyocardial biopsy we rarely do nowadays. A lot of the patients are diagnosed otherwise. But amyloidosis is a very heterogeneous condition. If the patient has heart involvement, and in severe heart involvement, the prognosis is very poor. So, this is an enlarged septum and you see the thioflavin stain with the amyloids right around the myocytes. This is the suggested workup. There is a lot of testing that needs to be done for amyloid

patients. The diagnosis is not difficult to make once you think about it. Think about it, please.

And in treatments, we treat the underlying plasma cell disorders and the disease is very heterogeneous. We could spend an hour just talking about amyloid treatment. But, we typically treat, similar as you can conceptually think about myeloma treatment, I would think that some of the agents that we more commonly use, up front, would be bortezomib, cyclophosphamide, lenalidomide, maybe not as much in amyloid, the tolerability is not as good. Transplant in some centers that could be a main way of approaching the disease, especially for patients maybe with one organ involved and otherwise healthy. The majority of patients, however, are not candidates for transplant. Daratumumab is a very effective drug for amyloid. I think perhaps more effective for amyloid than for myeloma, but recognize secondary amyloid. These are patients you're not going to treat, but you're going to refer to somebody who will manage their underlying rheumatologic condition better.

MS. FAIMAN So, with that, I just wanted to make a highlight, again. There are no FDA-approved drugs to treat myeloma and – or pardon me –

DR. BAZ Amyloid.

MS. FAIMAN There are – amyloid, thank you very much for that clarification – no FDA drugs to treat amyloid. But we do seek to eradicate the light chain clone. I think it's important to note too, many of our amyloid patients don't have a high clonal plasma cell percentage. So, if you're in a clinic and you see a new consult for MGUS and you're mild anemia and you're working that up,

they might not have a large percentage of clonal bone marrow plasma cells, but that index of suspicion should still be there with nephrotic range proteinuria or heart failure. And that will be evident in a study, near the end, and we're going to close out with this case study.

A 58-year-old school teacher with acute on chronic renal insufficiency. I like using that phrase. It was taught to me by an nephrologist. She had chronic renal insufficiency and had an acute episode where her creatinine spiked, has hypertension history, diabetes and hyperlipidemia; the usual. Had shortness of breath and bilateral lower edema. On examination, was in no acute distress, but you heard a little bit of a diastolic murmur. Heart rate regular, about 118, you think they're probably a little nervous to be there. Extremities with 2+ pitting edema and you're thinking is it because you're a school teacher and you're on your feet all day, or is something else going on? So, you draw a CBC and a chem panel. The CBC shows a little bit of anemia, platelets, and white cells are okay, but on the chemistry panel, you're like, what? This albumin should be like 4 and it's 2.7. Creatinine should be about 1.2, depending on your institution, it was 1.9 and calcium was normal. You check a troponin, just based on the increased heart rate and just because you saw Dr. Baz's lecture and said everybody should be thinking about amyloid if they have a protein and the NT-proBNP was really high, 3600. Serum free light chains were assessed and had a lambda free light chain that was really high, 3250, and normal is 19.4. Twenty-four–hour urine was mostly comprised of albumin and you're thinking, well, she has diabetes anyhow, but then you found some increased lambda light chain. Bone marrow had low

amount of clonal lambda plasma cells. Because of the high NT-proBNP, you check an echocardiogram, which showed a low global strain, showing a thickened myocardium. As Rachid had mentioned, I describe it to my patients like egg whites that get warmed or harden when you cook them. That causes a restrictive cardiomyopathy and it can also harden the kidneys. She had a baseline creatinine that was usually about 1.6, but went up to 2.2. And, she had had some renal insufficiency with her 5-year history. But, again, you're trying to decide, does this person have AL amyloid that needs treatment, and the answer is probably yes, because you do a kidney biopsy and there's amyloid there. So, the lambda light chain, you get a cardiology referral. She's started on torsemide and a beta-blocker for symptomatic improvement, a nephrology referral for the kidney amyloid, and then the education regarding diuretic management. So, it really takes a multidisciplinary team. You need the nephrologist, cardiologist, advanced practice providers, and of course your physician team. She was started with bortezomib, cyclophosphamide, and dexamethasone, or CYBORD. You provide instructions as to the diabetes and the mood swings and all the CBC and monitoring. And this person could do pretty well, if you get her heart failure under control, she's young, she could be a candidate for stem cell transplant because she's pretty active. This is just 2017 and I'm pleased to report that 2018 ASH will be out soon, but there are a lot of – daratumumab was big in the news last year. They had a nice pooled analysis of IMiD drugs, which do make a difference in myeloma, but are probably not as effective for – I keep saying myeloma. Amyloid. We're talking about amyloidosis. Amyloidosis, daratumumab,

I think is the hot topic. Bortezomib-based therapies with cyclophosphamide are very widely used, as I mentioned, though. And ixazomib is something that might be on the landscape.

This is the last slide before our closing slide. Again, just highlighting the importance of that collaborative approach to patients with plasma cell dyscrasias. From the diagnosis, the infusion, the financial with a social worker, etc., I think everybody should be involved.

So, in conclusion, there is an explosion of new therapies to treat multiple myeloma. And advanced practice providers, whether you're a pharmacist, physician assistant, nurse practitioner, nurse specialist, or just very active in your role, I think it's really important to educate patients and identify and intervene. How often, Rachid, in your clinic has it been, the nurse practitioner that comes to you and says this person has proteinuria, and then you discuss them and, you know, how do you work with advanced providers in your clinic?

DR. BAZ You know, and I've been very, you know, not because I sit here, but really, I've been fortunate to work with outstanding APPs. You know, I started actually working at the clinic with Beth, so I kind of, it a good role model –

MS. FAIMAN Ten years ago.

DR. BAZ – to start with. That was –

MS. FAIMAN Fifteen years ago.

DR. BAZ – that was a while ago. And 10 years ago. And, I think in reality, nowadays, you know, I have, you know, two awesome nurse

practitioners who work with me. And, in reality, if you think about it, a lot of the patients come not really to see me, they come – they've established this rapport with the nurse practitioners, with the nurses, with everybody in the clinic. And I think that it takes a little bit of a village to treat patients with myeloma. These are the patients who have chronic disease for a lot of them and you're going to establish this long-term connection with. So, it's really key to have this approach where everybody's involved because a lot of the time. My nurse practitioner or my nurse will say, "Well, you know, this patient, you know, this is, his wife is having a tough time. You know, a lot of visits will be difficult for them, now. Maybe we should think about an approach that's more portable," and this is some of the things that sometimes physicians are a little bit blind to.

MS. FAIMAN Excellent. Well, thank you so much. With that, I think Connie was going to come up and say something, but again, thank you so much for spending your Saturday afternoon with us. Thank you, Rachid for driving all the way down to Fort Lauderdale. Are there any questions? We have just a few minutes for questions. Like one minute, but we'll be here if you need to find us.

DR. BAZ Sure, go ahead. Speak loud.

MS. FAIMAN And if you have to leave, please feel free to go, but we're here for questions, if you'd like.

FEMALE I'd just wondered how long, or how often you do labs with someone on maintenance, like check the M spike, check the IEP?

MS. FAIMAN Rachid?

DR. BAZ So, for somebody on len maintenance, we have to do a monthly CBC per the package insert. That could be done, actually, off in the community. But in terms of myeloma monitoring, every 3 months, I think is appropriate, for some situations. What the –

MS. FAIMAN But looking at the kinetics of the disease, so in the first relapse or the first remission, they're not going to be likely, if they have good cytogenetics, they don't have the deletion of 17p, translocation 11;14 and 14;16 and all these other things, they should get a good long remission. So, as you mentioned, every 2 months is fine. But once they've relapsed, that likelihood of another remission in relapse is there and so you might have to do it a little bit more often. So, every 3 months initially, and then sometimes every 2 months or monthly if we're suspecting that slow biochemical disease progression.

FEMALE Just wondering if you have used doxycycline in AL amyloidosis and have found benefit for those patients with their poor prognosis?

DR. BAZ Well, we have used it. I have used it –

MS. FAIMAN In AA amyloid, I've used it.

DR. BAZ – and but it's difficult to use actually. It sounds like, you know, it's easy to tell a patient, well, take an antibiotic and it kind of maybe deceases some of the fibrin accumulation and dissolve some, maybe. But in reality, in my experience, patients have had a hard time with the GI side effects, and amyloid patients may be more susceptible to it. We don't have a lot of data that it's effective, so I think if I try it for some patients and they tell me, "Look, I'm

having trouble," I'll stop. But if they're able to tolerate it, sure, why not, it probably doesn't hurt.

MS. FAIMAN Mm-hmm. Yeah. Same experience here. And we have a few patients that have tolerated it. I'm not sure of the clinical benefit. It's one of those things that sounds really great, but we probably need a little more research until we can widely recommend it to everyone.

FEMALE Thank you.

FEMALE Thank you, Dr. Baz.

[END]