[MUSIC PLAYING]

RYAN HARE: So within my talk, I first want to review the myeloma bone microenvironment. I'll have a little overlap with Dr. Drake here. I want to discuss the bone preservation benefits of two classes of medications, one being the bisphosphonates. The second class being a newer medication called denosumab monoclonal antibody.

I think we all kind of recognize the bone preservation benefits of the bisphosphonates. But I think what people sometimes seem to put on the back burner, kind of forget about, is actually the antimyeloma properties of the medications. I mean, therefore every patient is being treated for antimyeloma therapy should be on some sort of either a bisphosphonate or a denosumab.

And really, the main focus of my presentation is on the medication selection and treatment tailoring for patients. Not all patients are obviously the same. In some patients, bisphosphonates should be used. In other patients, [INAUDIBLE] should be used. And I think sometimes this practical standpoint is kind of lost.

So my presentation will be a little bit of a different and more of a practical presentation on when to use what. So as Dr. Drake said, up to 90% of patients will have lytic lesions at the time of presentation. And really, this is secondary due to an imbalance within the bone microenvironment.

So when the plasma cells bind to the bone marrow stromal cells, there'll be an increase in cytokines, specifically interleukin 3, interleukin 6, RANKL, and macrophage inhibitory protein 1 alpha. This will augment and ramp up osteoclast activity. But there's also a coupling at the same time with an increase of cytokines that will decrease osteoblast activity, including sclerostin, dickkopf family of proteins 1, and then secreted frizzle related protein 2.

So in essence, the myeloma patient with the coupling of the plasma cells within that bone marrow stromal tumor cells, it just is a natural imbalance in the bone resorption and building process. So as we all know, the bisphosphonates will help preserve the bone by adhering-- it adheres at the bone matrix itself.

And it will decrease osteoclast activity at that site. But it also will induce apoptosis of preosteoclast. This results in decrease in pain from fractures, prevents worsening of ECOG scores, and will preserve the overall quality of life in myeloma patients. But I think what also we need to focus on, and I think what people-- I think sometimes we forget about this-- is that the bisphosphonates themselves actually helped treat the myeloma.

And the way that they do this is they just disrupt that coupling and that binding between the myeloma cell itself with the bone marrow stromal tumor cells. So by inhibiting that coupling, you will decrease the release of all those cytokines that I showed on the first slide, which will prevent the invasion of the myeloma cells into nearby bone.

Also it inhibit the adhesion and migration itself. So this secondary inhibition will further decrease osteoclast activity and promote osteoblast, ultimately having the patient live a-- or have a more normal bone resorption and building process. Important thing to note, though, is not all bisphosphonates are created the same.

So there's first-generation bisphosphonates, and there's a second-class, or a second-generation, bisphosphonates that contain nitrogen. The nitrogen-containing bisphosphonates are thought to exhibit antimyeloma properties, or the non-nitrogen containing ones do not.

There are some oral bisphosphonates that do contain nitrogen. But unfortunately, oral bisphosphonates are really hard to be compliant with. They have poor absorption. And really, in multiple myeloma, they, in my opinion, they should not be used. The intravenous ones-- nitrogen-containing bisphosphonates should be used.

I think it's fine in [INAUDIBLE] patients. But people with active myeloma should not use the oral versions. With patients that are presenting with hypercalcemia of malignancy, zoledronic acid has been shown to be superior to pamidronate. So in this particular patient group, a flat dose of four milligrams, not renally adjusted, should be used in this particular patient population.

So here's an image of the bisphosphonates. Unlike the CAR T-cell therapy, these are not exciting at all. They're actually very basic, very basic molecular structure. They get their name because they have two phosphate groups on the other side of a carbon atom.

If you see on the right-hand side, I have pamidronate. And if you notice in the bottom there-- I don't know if there's a pointer here-- but-- does this point? But it has a nitrogen-containing group. And then also zoledronic acid, you'll see that it has two nitrogen-containing groups.

Alendronate and ibandronate, you'll see that they also have nitrogen-containing groups. But as we mentioned, because they have such poor compliance, we really should stick to pamidronate zoledronic acid, if possible in multiple myeloma patients. And the other two bisphosphonates up there, etidronate and clodronate, are not thought to have any appreciable antimyeloma therapy and therefore should not be used in people with active myeloma.

So I just want to focus here on the bisphosphonates selection and tailoring for patients. So as we all know, pamidronate and zoledronic acid can cause renal failure, are toxic to the kidneys. But they're toxic to the kidneys in different ways.

What people don't realize is zoledronic acid exhibits an acute tubular necrosis, where pamidronate is toxic to the kidneys in more of a focal or segmental focal glomerulosclerosis. So with pamidronate, that type of renal toxicity is actually dependent on how high the concentration is.

So you can get around. So in patients with severe renal impairment, which is defined as a creatinine clearance less than 30, you can use pamidronate and actually just drop the dosing down and infuse it over a long period of time. I think oftentimes we do that in clinic. I don't think of why we do it or the underlying mechanism.

But pamidronate, if you are going to use a bisphosphonate in someone who has severe renal failure, you can just infuse it slower. And it should be used. Where zoledronic acid should not be used with anyone with a creatinine clearance less than 30. It should be noted there's no data on the use of bisphosphonates in dialysis patients.

And we do have a newer medication that just came out called denosumab. So you could always consider-- and this is really I think our main utility at Roswell. And we do use denosumab. We still mainly use the bisphosphonates. But in patients that have a creatinine clearance less than 30, this is the main utility of this newer agent.

So to understand how denosumab works, we have to understand the underlying RANKL pathway. So RANK ligand is essential for osteoclast formation, survival, and migration. So as the plasma cell will bind the bone marrow stromal cells, it'll increase the amount of [INAUDIBLE] RANK ligand but also ligand binding to the bone marrow stromal cells.

If you see here as that [INAUDIBLE] RANK ligand and also the RANK ligand binding to the cells, attached to that RANK receptor on that osteoclast precursor cell, this allows for the promotion to a mature osteoclast. At the same time, so not only is the plasma cell promoting production of osteoclast, it's looting-- a defense mechanism by secreting CD138 there, which will bind to a natural dummy receptor.

So we have osteoprotegerin, which is a natural dummy receptor, which will bind up RANK ligand. So it's a two-fold increase in the risk of fracturing. So not only are you promoting osteoclast, but you're also blocking the natural ability to bind up [INAUDIBLE] RANK ligand.

So denosumab is the first of its class. It's a fully human monoclonal antibody that neutralizes that RANK ligand. This was studied in 1700 newly diagnosed multiple myeloma patients that had presented with at least one lytic lesion. This is a double-blind, randomized, phase-3 control design.

It was a noninferiority trial, with half the patients, roughly half the patients, receiving denosumab and the other half receiving zoledronic acid. The primary endpoint of this study was a time to a skeletal-related event. And for that primary endpoint, the researchers found that there was no difference-- or it was not inferior, I should say, zoledronic acid in that time to a skeletal-related event.

The two most concerning adverse effects of these agents-- one is osteonecrosis of the jaw. The other being renal impairment, most notably with the bisphosphonates. They didn't see a significant difference between either side. But it should be noted people that had a creatinine clearance less than 30 within the study were excluded.

And they had to be excluded because you can't use zoledronic in that patient population. So for denosumab, for us, I think, we use it the most in patients that have acute renal failure. It should be noted this medication is more likely to cause hypocalcemia compared to bisphosphonates.

So everyone that goes on denosumab, I think sometimes it's easy for people to forget that calcium and vitamin D, they should be on. But these people should absolutely be on calcium replacement because it's much more common in the bisphosphonates. And really, the people that are getting bisphosphonates as well should be on calcium and vitamin D therapy once the calcium itself has been stabilized.

This last point is actually really important. And this is a reason why we don't exclusively use denosumab. And it's because you can't abruptly stop it. If you abruptly stop denosumab, there's an increased risk of multiple vertebral fractures. It's not completely understood why this occurs.

But I kind of theorize that unlike the bisphosphonates, which hang in the bone matrix for a long period of time, we don't see that as long of a period time with the denosumab. So if you abruptly stop it, you have a transient burst in RANK ligand and subsequently a transient burst in osteoclast.

This hasn't been proven. But I think that's why we don't see it with bisphosphonates. It's just because it just hangs out in the bony matrix for so long. So it wouldn't be a talk about bisphosphonates if we didn't talk about osteonecrosis of the jaw, which is one of the major concerns with these medications and also with denosumab.

So it hasn't been confirmed yet with denosumab. But with the bisphosphonates, the average time to osteonecrosis of the jaw, or ONJ, is two years. We do know that cumulative dose increases this risk. And so use beyond two years really should be based on clinical judgment.

But there have been a couple of studies that show that you can actually give the bisphosphonates a little less frequently. And there's actually not an increased risk of skeletal-related events. Now these studies included the one-- one of the multicenter trials was here. And it did include some myeloma patients.

But this also included solid tumor patients. So really, every patient's different. We have to adjust here at Roswell. Well, our standard of care is generally to accommodate both the safety aspect of these medications but also to make sure we're augmenting the antimyeloma properties and preserving bone. Is to give the bisphosphonates at a two- to three-, four-week frequency for a year.

And then after a year, to back off and give it every three months based on these trials. And we'll actually exceed that two-year judgment-- or that two-year cutoff in most patients. Now it should be noted-- this is specific to the bisphosphonates-- the denosumab, you have to give it on a two-month interval.

You can't give it every three months. I mean, you can back off. But there's no data in multiple myeloma patients in doing that. And really that risk of that multiple vertebral fractures would make it so you wouldn't want to give it too infrequently in myeloma patients.

So decrease the risk of osteoporosis of the jaw-- all patients should have a baseline dental exam. And all invasive procedures, if they require, should be done prior to treatment start. If at any point during treatment a patient has to have invasive dental procedure performed, here at Roswell we will hold the bisphosphonate therapy or denosumab therapy for at least three months prior and three months after.

And the unfortunate patients that develop this side effect, treatment includes oral surgery in severe cases to get rid of the necrotic bone. In less severe cases, we can use antibiotics and just try to increase blood flow to the area using a drug called pentoxyfylline, which will just vasodilate.

So I keep my section short. And really, I think in summary, I think bisphosphonates at this current time should remain the standard of care for most patients. And denosumab has its spot in therapy. And really, for us, it's when people have a really poor creatinine clearance.

[MUSIC PLAYING]