[MUSIC PLAYING]

JENS HILLENGASS: Now we heard about very sophisticated things to go very in-depth in the biology of the disease and genetics of the disease. Now it's become a little bit, I think at least in my small mind, it becomes a bit easier because I'm discussing imaging.

But I think it's still very important. We have all the sophisticated analysis techniques. We can learn more. And you will hear more about this during the day, about mass spectroscopy where we can learn more about the monoclonal protein. And in other areas, we learn more about single cell sequencing and stuff. But it's still, for our patients, it's very important that we and they know what's going on in their bone, what's going on in their bone marrow. And as you've heard from Max, it's also important where we put the needle to get the real biological information. A few disclosures.

A lot of you might have seen this slide because we are really blessed with a lot of new treatment options that we can offer our patients. And over the course of the years and the last decades, we saw really tremendous improvement. And it's becoming more and more dense at the end because we have so many new drugs that have been approved. And you will hear more about that later on. But it's also the case that we have more sophisticated imaging techniques.

So we know myeloma is a disease of the bone marrow. But the symptoms, or one of the major symptoms, as you know, is a bone disease, the osteolytic lesions. So looking into the bone marrow, we usually do with microscopy after we did a biopsy. But looking at the bone is usually the domain of imaging.

And I always try to start, to kick off my talks about imaging with this clear differentiation between bone and bone marrow. Bone marrow is where the disease takes place. Bone is where the symptoms take place. So this is disease. This is symptoms.

What we want to know if a patient comes to us and we have the suspicion of myeloma, we might even have done a bone marrow biopsy, we have this matching more than 10% plasma cells, even though no one really knows if 10% is the right number. But we say, OK, this patient has a myeloma. Now we want to know what's going on in the bone.

So the extent of the bone disease is very important, the bone destruction that has already happened. Because oftentimes, as you know, a lot of our patients come to us with back pain, with fractures. And we have to figure out what else is going on in their bone.

We want to know if there are any risks for new fractures, so the stability of the remaining skeleton. We also want to see if they have osteoporosis. Is this related to their myeloma? Or is it related to something else? Because osteoporosis is also something that happens in our patient collective that is more, of course, more of our patients are older. And so it's very important to also differentiate where the bone disease is coming from. Is it really myeloma or is maybe something else?

In the bone marrow, we can do the bone marrow biopsy. We can do our serological markers. But we can also look into imaging and see how far distributed is the bone marrow involvement by monoclonal cells. And I will show you why imaging can be helpful with that.

And of course, we want to know if those patients have soft tissue tumors because that might also change something because those cells have managed-- usually, myeloma cells, if you take them out of the bone marrow, they die rather early because they need this microenvironment, this nurturing of the neighboring cells. And so if they have a soft tissue tumor, if they even have, as Max already mentioned, a plasma cell leukemia where the cells survive in the peripheral blood or in the soft tissue, then this is really-- that tells us a lot about the aggressiveness of the disease.

And I just love this study because it's older than myself, which is not why I love it. But we should know that for a really long time, they took a spine of a corpse and they drilled holes into the spinal bodies. And they filled them with water and then did an X-ray. And they looked at how much of this [INAUDIBLE] body do I have to destroy until I see a change in X-ray. And it was actually 30% to 50%, in some areas 50% to 75%. So almost all of the bone was gone and then they saw something in X-ray.

So when I came here to Roswell I was surprised that this really high end clinic still used X-ray. Just teasing. But it's interesting that we have this low sensitivity technique but on the other hand, we used CAR T-cells to treat our patients. I mean, come on. And I changed it. It was my first act here.

And this is actually a patient that we saw here, had pain in her hip. She's just going for transplant now. And she came from outside. And she had her X-ray of the pelvis because that was, at that time, still standard of care, like half a year ago before Saad and I published the new guidelines.

And so it looks, basically, to me it looks normal. But then we did a CT because I like CTs. And what you can see here in this area, there's almost no bone left. So there's a huge tumor growing out of the bone. And this is really, literally, a few days later. The left side is an X-ray a few days before the right side.

I have seen a lot of images. But I see nothing on the left side. I mean, it's OK. n equals 1, so it is one patient. But for me, that was really kind of the confirmation that we are on the right path to say, not only do we have to improve our treatment, we also have to improve our diagnostics.

And we did an analysis where we asked people from the whole international myeloma working group to send us images where a patient, for whatever reason, had a CT and an X-ray at the same time. And we had over 200 patients. And we looked into them and we found that about 25% were negative in X-ray at the same time they were positive in CT.

So 25% more sensitivity, more or less. And those were patients with MGUS, smouldering myeloma, and myeloma. So this is really 25% more. I think it's really significant. And the p value, as you can see, is really significant.

And this is how a whole body low dose CT looks like. It gives us not only the information on the bone. It also gives us information that oftentimes we have not asked for, which causes sometimes trouble because [INAUDIBLE] and I and our fellows have to work up things that we didn't want to know. But sometimes we find even more things, which is, of course, not always of benefit for the patient. Because sometimes they're scared. But it gives us more information about the disease.

And I will come back to the issue of stability. CT is the best technique to give us information on stability. In some cases, MRI is also very helpful. But these newer techniques really give us a much better insight. I have to say, when we started to change-- back in the day in Heidelberg, when we changed from X-ray to CT, we found so many more osteolytic lesions. We found so many more patients with, really, issues in their cervical spine, which was really scary in the beginning.

I mean, those patients had the same myeloma than the patients before. But it was sometimes really scary to see how much tumor is really there that we missed in the x-rays. So it doesn't help to just close our eyes and say we just use the less sensitive technique because it doesn't make us work more. I don't know.

So stability is, I think, a major thing. And we have to make sure-- as soon as we know that a patient has multiple myeloma, we have to make sure they don't have more bone issues. Of course, they might have more pain. They might have maybe even a fracture that is not progression. But our job is really to make sure that they don't have more issues. And there is also, actually, pretty old data already about the stability of the spine, how we can assess that, not only in myeloma but also in solid tumors.

If for example, if the vertebral body is collapsed more than 50%, obviously that's not good. If both pedicles are involved, that's also not good. Because that's something that I learned over time. They are very important for the stability and also for the protection of the spinal cord. Involvement of more than 50%, not only fracture but also involvement of more than 50%, and you can see that on the right side where a patient really has that.

And destruction of anterior and posterior parts, meaning there is an instability in the-- as you know, we always move our spine. And these forces that are putting pressure on our spine, they can be very heavy. And as soon as we lift something-- and my physics days are long gone-- that can be really dangerous for our patients. So we really have to make sure that we know what's going on in our patients.

I already mentioned that we sometimes have, for example, the elderly lady with an MGUS. And she's post-menopausal. And then we have to figure out, she has an osteoporosis, is this myeloma related, which would cause us, of course, to treat her. Or is it just a benign osteoporosis that can happen?

And MRI is very helpful in this case. Because MRI gives information-- MRI measures, basically, the water content of the tissue. And if you have a high water content, this usually means more cells. If you have a lower water content or a higher fat content, which is kind of the opposite of water in MRI, then you can say, OK, a high fat content is most likely not myeloma related because that's usually, when we get older, our bone marrow is replaced by fatty marrow. So high fat content, rather benign osteoporosis, and maybe even fracture, and high cellular content is rather multiple myeloma or another cancer. So this is very helpful. And it's a pretty easy technique to use.

I mentioned the tumor burden and also that myeloma is not always growing the same way. And you heard a lot about that already from Max. And we, together, actually work on this topic for quite some time now. We have some patients whose spine, on the left, looks basically like a normal spine and still they have multiple myeloma. They might have more kidney disease. They might have more anemia.

Others have this diffuse infiltration, as you can see in the middle. This is much darker. And darker is called hypointense in radiological speech. And they have a very high cellular content. They have a lot of water in there so a lot of cells. And this is a very heavily infiltrated myeloma. And we know that oftentimes, for example, plasma cell leukemia patients look exactly like this.

And then some patients, as you can see, have those dark spots. We call them focal lesions. And this is exactly what causes the trouble. Because, as Max mentioned, if you put a needle in there, it might be a completely different result than if you put a needle somewhere else. So this is very important to have this information. And we get this information from MRI or from PET because they show the bone marrow, as I mentioned, the realm where the disease takes place.

And we looked into different areas in MGUS and smoldering myeloma and multiple myeloma. And what we found over and over and over again is more tumor is worse, which is, again, not a surprise. Because we know metastatic disease is not great. But this is what we found, more focal lesions really is a higher tumor burden. And this causes an adverse prognosis for the patient.

But sometimes we are surprised that we have a patient with focal lesions and this patient has no problems at all. So we have to make sure that those focal lesions-- usually, if there are hundreds, then it's clear. But if there are like two or three focal lesions and we see this patient, this patient is feeling great, has no other issues, doesn't fulfill any other criteria, then we usually recommend to repeat the imaging. Because what we have learned over time-- and [INAUDIBLE] working with this group a lot on that-- the dynamic of the disease is oftentimes more important.

And we had this discussion this morning when we were visiting Niagara Falls together. To add to the complexity, this spotlight on one time point is oftentimes not enough. We find maybe two or three focal lesions. And according to our new guidelines, we would have to treat this patient. But we look into patients before that, retrospectively before we had these new guidelines, and looked if patients had a smoldering myeloma and had several imaging examinations over time. And we found that if those focal lesions, if they were there and they were stable, or if they had no focal lesions at all, of course, and they didn't develop anything, then they had a very good prognosis. This looks like MGUS.

And then we had other patients who had either none in the beginning and then they developed focal lesions or they had focus lesions and those grew or became more in number. And they progressed rather rapidly. And that's very important because not only looking at one time point, but sometimes it really makes more sense-- and the same is true with [INAUDIBLE] light chains and other techniques that we have. If it's really not clear, then I would rather repeat this, especially if the patient is feeling very well. So it's important to differentiate between dynamic disease and stable disease.

And we learn more and more that-- and a lot of us talked about that. We agreed that there's actually MGUS and myeloma. There's not really smoldering myeloma. Even though we give this attribute to some patients, there's no real smoldering myeloma. Either we have called the real myeloma early, that's a smoldering myeloma, or we have an MGUS with a little bit more tumor burden, then it's also smoldering myeloma. But it's biologically either MGUS or myeloma. So that's something that we learned with the dynamics of the disease and also other factors over time.

And here's a patient, for example, just to show you how that might look like. We had a smoldering myeloma and we had no focal lesions. We said, everything is negative. We did a CT and an MRI both. We were basically negative. So we went on. This is just to see better.

And then all of a sudden, like six months later, this patient had this-- I don't know if you see that-- this brighter spot, which in this sequence is a focal lesion. It's a T2 imaging. There they are bright, not dark. So this bright lesion occurred.

And so we thought, interesting that something new develops. And we thought, maybe that says something. So we found this. And then we looked back and if you look very, very closely-- and our radiologists in Heidelberg, they have seen like hundreds and thousands of MRIs. And they didn't see that and we didn't see that either, of course. There's a tiny little focal lesion if you know where to look.

And we saw there's a dynamic. This is growing. And then we did a CT giving us information on the bone and actually there's an osteolytic lesion. So this is kind of this development, that's our theory right now that those focal lesions, when they grow and when they develop further, all of the sudden they cause osteolytic lesions.

And we looked in this first study where I showed you the dynamic versus stable. We looked into the reasons why those patients progressed. And if they had progressive focal lesions, more focal lesions or growing focal lesions, most of them, you can maybe see this small piece in here. B means bone disease and A means anemia.

Most of those patients actually developed bone disease afterwards. So I think this theory is very valid that focal lesions develop into osteolytic lesions. And if we know about focal lesions, we have to be very careful that we can avoid further fractures and further bone destruction.

Of course, extramedullary disease. At first diagnosis, this is very rare. But since we use better imaging, we see more patients, obviously, with soft tissue tumors. But later on in the treatment of the disease, as I said, we select those worse clones, those bad clones, and they tend to develop more soft tissue disease. And this is something that we have to be very aware of and be very careful.

After treatment, what are questions there? Of course, we want to have a remission that is as deep as possible. But if you do serological markers, they are negative. Immunofixation is negative. If you do bone marrow biopsy, they have less than 5% plasma cells, great. Complete remission. But if you then do a PET-CT, for example, and you find residual focal lesions, those patients are not really a CR. They still have some disease left.

Heterogeneity of response, we have some patients who respond in some areas but other areas are the same. And actually, I talked to [INAUDIBLE], who was in Arkansas, and looked into their imaging database. They have hundreds and thousands of patients. And he saw that some patients even developed a relapse at the point where we thought we had treated them and maybe brought them into complete remission. And at that time point, they already developed the new lesions with these more aggressive clones. So that's important.

Soft tissue tumors, I already mentioned. And bone healing is something that we also see since we have more sophisticated techniques. And I will show you image for that. So these are just three studies where they looked into the relevance, the prognostic relevance, of residual lesions.

And all of them you see, with very strong statistically significance, showed that if you have no residual lesions left, your prognosis is much better than if you have residual lesions, which is again not surprising. We do that in lymphoma. We do that in solid tumors. But here it's in myeloma. This has been shown several times by several different groups.

And this is something that I already mentioned. If we do an MRD assessment or a CR assessment with the bone marrow biopsy, this patient might be MRD positive here and MRD negative here. That doesn't mean that we have to do a CT guided biopsy in all of our patients. But it's something that we should keep in mind. And Ola will talk more about the MRD assessment. So we have to be aware that putting a needle in one place in our myeloma patient might not really tell the whole story.

And there's actually data from the French group showing you can be PET-CT positive, PET-CT negative, and MRD positive, negative, whatever. You choose your combination, it's there. And if you are double negative, meaning your imaging is negative and your MRD is negative, then you have a very good prognosis. And those curves, they almost look like Hodgkin's lymphoma.

So we're getting there. We have good treatments. But we really have to make sure that our patients are in a deep remission. At the moment there's no recommendation to change a treatment or to go on with the treatment, other than the general recommendation that we do maintenance treatment. But there are studies in development to really see if we have residual disease after treatment, should we change our treatment to really go further and bring the patient in a deeper remission. And these are two different studies showing if the double negative, that's obviously very good.

Interestingly enough, if you have an imaging negativity, meaning no residual focal lesions left, and even if you have a high risk disease, as you have heard like, FISH high risk, GEP high risk, then you also have a better prognosis. So that will come back, I guess, this discussion later on when we talk about MRD.

So achieving a deep remission with whatever treatment we give the patient can kind of, in some patients, override the high risk character of the disease. So this is also very helpful. And again, we have to treat our patients very effectively in the early phases of the disease.

We have a new technique called diffusion weighted imaging, not that new anymore. It's actually an old technique that they use in brain tumors. It basically, again, looks into the water content of the tissue. And it looks into how far water molecules can move. And an MRI machine can measure that with some software tweaks.

And if you have a lot of cells, the lipophilic cell membranes can restrict the chance of the water molecules to move. And if you have a lot of necrosis and dead cells, then the water molecules can move further. And we have kind of different shapes between high and low cellularity. And this has a very high sensitivity.

And this is how it looks like. And a colleague from Heidelberg called it the poor man's PET. It actually looks like a PET. But it has no radiation exposure, no contrast agent. And these are, basically, on left side is before treatment. On the right side, just after induction before high dose. You can see that there are less lesions and they are shrinking. So this is what we see over time when we treat our patients.

I mentioned the bone healing. Not every patient shows that. But some of our patients, since we do CT, we see that some patients, this is the osteolytic lesion before treatment. This is the same osteolytic lesion after treatment. And you can see the body starts to build a sclerosis around the osteolytic lesion. So there is kind of a bone healing.

And I think we see it since we have more sophisticated imaging. But we also see it because our treatments are more effective. So this is something that's very nice. And oftentimes, I like to show that to our patients to kind of encourage them that what we are doing really leads to visible tangible results.

So in summary, I would really, really strongly recommend CT better than X-ray. And if you have issues with reimbursement, and we do, too, we are working on the CPT code. At the moment our radiologists are able to get this reimbursed. So if you need to send a patient, please do so. We can do a whole body low dose CT.

Stability assessment, very important at first diagnosis but also at relapse. PET-CT or diffusion weighted imaging are great for residual disease assessment. So this is something that we should keep in mind, not only do the biopsy but also look into the whole, with a lower sensitivity, but in the whole body. Imaging should be combined with MRD assessment. If we want to really cure myeloma, we really have to prove there is nothing or at least nothing that we can measure left.

And with this, I thank you for attention.