Cardiovascular Toxicity and Immune Checkpoint Inhibitors

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Dr. Bell: Welcome everyone. My name is Malcolm R. Bell, M.D. I'm the vice chair of the Department of Cardiovascular Medicine here in Rochester, Minnesota, at Mayo Clinic. And this is another episode of our interviews with the experts. And I'm very pleased today to welcome and introduce my colleague, Joerg Herrmann, M.D., who's the director of our Cardio-Oncology Clinic. And he's here today to talk about immune checkpoint inhibitors and cardiovascular toxicity. Joerg, welcome.

Dr. Herrmann: Thank you so much. Yeah. It's exciting to be here and a great opportunity.

Dr. Bell: Yes, indeed. So I think one of the first questions many of our viewers will have is, what exactly are the immune checkpoint inhibitors and what are they used for?

Dr. Herrmann: Yeah, immune checkpoints, they're really an integral part of the immune system in all of us, in fact, making sure that there is no overactivation once an immune response is triggered. And there are two main systems: One is called CTL-4. That's expressed on T cells mainly in the thymus as they get primed by antigen-presenting cells. The other is more in the periphery and that's the PD-1, the program death receptor, PD-1 and PD-L1. The T cells, again, express the PD-1 and then the tissue is expressing PD-L1. So now tumor cells, as smart as they are in their own ways, have found a mechanism to express this PD-L1. And PD-1. So that silences the T cells as they come and are about to attack the tumor cells. So it's a very sneaky mechanism. And the immune checkpoint inhibitors now were developed, I mean, it's sort of, serendipity, that for most discoveries in medicine, as it is here, there is, there are fascinating stories to how this came about. But there are now three FDA approved for PD-1 and three approved for PD-L1 antibodies as well as for CTL-4, so we have a total of seven approved immune checkpoint inhibitors which really were, are interfering with this, with this action of the, or can you call it the natural brake in our immune system. So what this does in terms of a tumor response is really unleashes these T cells. They are no longer silent. They will attack the tumor and with really dramatic responses. And so it has been revolutionary, Malcolm, I can only say that.

Dr. Bell: Yeah, I mean, it's really fascinating. That sounds like a little microcosm of a war going on here. But, so did I hear you say, then, that these would potentially then enhance program cell death?

Dr. Herrmann: Well, I mean, yeah, it's supposed to. I mean, like it's like Star Wars, right? I mean, when the troops are marching in and they're supposed to, yeah, that's what the T cells do and they're fascinating as a group and, if you've ever watched that video, how a T cell that recognizes and attacks a tumor cell, injects the lytic substance, this poisonous material, it's really fascinating. But on the flip side, I mean, as you can imagine, that can also go rogue, right? I mean, this can then affect your own healthy cells unless they're otherwise protected.

Dr. Bell: Before we get to that, maybe just briefly tell us what type of tumors are these used for. I assume that it's going to be used for very serious malignancies, advanced malignancies. But what are the common malignancies that these are being used for and how much of a difference do they make in outcome of these patients?

Dr. Herrmann: Yeah, I mean, so fascinating story. I don't know if you remember Jimmy Carter. Years ago, he had metastatic melanoma. He was already advanced in his age; I mean he was very senior back then. And so he was one of the first to receive what's called pembrolizumab. Keytruda is the brand name. And within a month, you already, you had the noticeable response, you had liver and brain metastases and then a few more months in these were all gone. And so we have now about 20% of these metastatic melanoma patients who will see this complete response. It takes about six months of therapy and they have a durable response. What the majority, but this was something unheard of, and so the first pivotal trials in this area were done in melanoma patients, metastatic melanoma. And they really doubled the survival rate even over what, what best.

Dr. Bell: Obviously, sorry to interrupt you. I mean, obviously Jimmy Carter is still around, so it's obviously had a long-lasting effect. But some melanoma, other tumors that it's used for?

Dr. Herrmann: Yeah. Lung cancer is a predominant example. Head, neck. It's been expanded now to 50 cancers. We have 3,000 trials that are looking at sort of like T cell based therapies. There's a legitimate concern that we're running out of patients for all of these trials. It really has exploded. So it's a major revolution.

Dr. Bell: Well, thanks very much for that background. That's very, very helpful and nice to get that in a nutshell. So let's now talk about really what we're here to talk about there is, what's the downside of these drugs? And obviously there's toxicity associated with any drugs, and particularly chemotherapeutic agents. But with respect to cardiac toxicity of these agents, tell us about what we should be looking for there and how often this might occur.

Dr. Herrmann: Yeah. So that has, relatively soon, actually, received quite a bit of attention. This potential cardiovascular toxicity that we can see. And one might think of this being more of a surprise than we initially thought. Because when we think of all these different inflammatory scenarios in cardiology, we often think of maybe pericarditis. We think of maybe leading to some flourishing atherosclerosis with more acute coronary events. While we see those, I mean it's not that common. What's really got the attention is myocarditis. And so it's not one of the most common, in fact it's one of the least of all this "itis," we call it immune-related adverse events. Maybe 8% of patients. But there might be a large subclinical figure that's not captured because there's no routine testing necessarily. But what the aspect is, it's not the most common, but it's the most commonly fatal complication in 40 to 60%. And it was those cases of fulminant myocarditis that really got the attention and that's just the tip of the iceberg. But that, like ever since, I mean, everyone is really sensitized to this possibility.

Dr. Bell: Sure. So the least common but the most fatal. And so presumably this presents just like a myocarditis. Your typical myocarditis, I mean, in terms of heart failure, arrhythmias? I mean,

how do you diagnose it? Is there anything special that we should be looking for? And then, is this something that is dose dependent, or could it occur after the first dose of one of these agents?

Dr. Herrmann: Yeah, I mean, that's an excellent question. It's, actually most of these cases occur within 30 days of treatment. I mean, not uncommon even after the first dose. So there's something that's already preexisting we believe. And it's sort of then just unleashed or the brake is taken off. But the exact mechanisms have not been defined. It presents itself a little bit like sarcoidosis with what you've just mentioned, I mean reflections of the irritation of the myocardium. So arrhythmia is usually a warning sign. If there is any type of heart block newly developing, atrophy, VT. Atrial fibrillation; we've seen that, too. But especially in the beginning when we saw our first cases or the oncologist saw them, patients would present with weakness. And I mean, and you know, they don't take routinely and then all of a sudden they would have a low heart rate.

Dr. Bell: Yeah. So that's really important to understand because you have people who are sick, who may be feeling weak and maybe they have some what appear to be minor arrhythmias and, but if we see that, I think you're trying to tell us that we should be thinking about your possible early onset of myocarditis.

Dr. Herrmann: Yeah. The other aspect, Malcolm, is that they have, I mean, often profound myalgias because myocarditis in myositis often go together. And we've noticed a number of patients complain of back pain. And it might be because the spinal musculature, I mean, it's so integral to all of us to keep upright. And then other phenomenons are types of neural involvements. It could even be the eye muscles. In that really, I mean, is involving muscles and showing some abnormality or some symptoms should already raise some suspicion.

Dr. Bell: So, clearly someone with fulminant myocarditis, we're admitting that patient to hospital. What about these some of these other ones who have these more minor complaints say, how would you work those up? But again, we only have a few minutes left here. Are we looking for biomarkers, are we doing echos? Could you just give us a quick rundown of how we should evaluate that patient in the outpatient setting.

Dr. Herrmann: Right. And so it's felt that biomarkers troponin in BNP or NT-proBNP are the most useful in the setting. With BMP you get a reflection also of a potential cardiomyopathy without inflammation, which we've also seen, takotsubos, even. So it's some form of cardiac dysfunction. Now, this being said on the echo things might look, other than if it's takotsubos, might look relatively normal, even in cases of fulminant myocarditis, until the decompensation point. It can look a reassuringly, falsely reassuringly, normal. And so troponin would be, mean from myocarditis standpoint, would be the way to go and they don't need to be extraordinarily high. We've seen cases with VT, MRI-confirmed myocarditis. And the troponins were maybe just in the double-digit or three-digit numbers.

Dr. Bell: You're talking about high-sensitivity troponins.

Dr. Herrmann: High sensitivity troponins, yes. And that's what most people are using these days. Well, there needs to be a level of attention. And then syncope is the, I forgot to mention earlier,

syncope is something that really if patients start to complain about dizziness, definitely something to look into and from other clinical signs, wen do I need to be worried about is when they complain about shortness of breath or a hypoxemic, those of you that have pneumonitis on top of it or they really have something so prominent that they're on the brink of decompensating more quickly.

Dr. Bell: And so this is really where you bring in someone like yourself, a cardio-oncologist, Joerg, who is really primed to look for these things here. And again, you know, time is running out here, but maybe, is this treatable? Does it respond to high-dose steroids, other immunosuppression?

Dr. Herrmann: Right. Right. The recommendation is there's a high level of suspicion that it is high-dose steroids. One gram of solumedrol, that's usually what most would give. Some continue after just giving one dose until the workup is complete. And in fact, I might add, I mean, it's not just getting an echo or cardiac MRI. Cardiac MRI is preferred. In fact, the yield of the cardiac MRI is higher the longer you wait after an admission for suspicion. And it's been shown that after a few days, I mean, it turns out to be more positive than doing it right away. And then those who were still suspicious, but there's no concrete diagnosis yet, a biopsy. I think we were very reserved in the beginning. And so with all of this in place, so and then if there is the evidence, then you definitely want to, if you need to have to accelerate beyond steroids. So you need to be in a position ready if the steroids don't do the trick within two days or three, the patient is deteriorating — we've seen cases go on ECMO, even — for patients to come through. It is possible to bring them through, but you need to be prepared to accelerate to more aggressive therapies.

Dr. Bell: That's good to know that eventually the outcome may be fairly good, from what you're saying. What about a patient who has maybe just mild symptoms, not full-blown myocarditis and maybe minimal elevation of troponin. But really it seems like this could be cardiac toxicity. Does this mean then that the structure be permanently discontinued? And obviously that's possibly quite devastating news for someone who's got advanced malignancy, who has their hopes pinned on these revolutionary drugs.

Dr. Herrmann: Right. And that's unfortunately not fully defined yet. I mean, fortunately with a 1% incidence, I mean, we haven't had that many patients where we could test this out, so to speak, to rechallenge if they're not in extremis. But the recommendations are if it's in, the oncologists think in terms of great grades of toxicity, like one is very minimal and five is lethal. So a grade 3 to 5, so moderate to severe, the recommendation is not to resume, but on a case-by-case basis, and I personally, if anyone has shown sign of anything life-threatening, I think it's hard to argue. You would try to redo that, right? But how would you predict if someone who had early signs, as you mentioned, some mild troponin elevation? And then we got a cardiac MRI and we see myocarditis, but they are otherwise fine. How shall we deal with those? I think most of us would say we would still treat until the evidence is gone. And then it's going to be a shared decision-making. If there are no other options for the patient, is the patient willing to take the risks to re-expose given how the story went the first time. And that's something we need to learn as we go.

Dr. Bell: Okay, Well, that's all we have time for this session, Joerg. I really appreciate you providing these really important insights. And I think it does emphasize that for these patients, I mean, obviously these are unfortunately rare events, but they're often going to be in younger patients. And obviously the complications, you know, can be life-threatening and fatal in some. And I think it does make the case for really having specialists like yourself, who are cardio-oncologists And, and so I think one of the messages here would be that for specialists like yourself that need to be reached out to when faced with these really, what would be devastating, you know, complications.

Dr. Herrmann: No. I said in the beginning I appreciate definitely a platform. I think we're always available. But this is a topic that every cardiologist needs to know about. Every internist, maybe even every ER physician, right? Because if a patient comes in with that history, and it can make the difference, as you pointed, between life and death.

Dr. Bell. Ok, well, thanks very much, Joerg, and I'm sure all of that viewers really appreciated hearing what you had to say about this. So thank you very much and thank you, everyone, for joining us today.

Dr. Herrmann: Thank you. Yeah.

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