Immune Checkpoint Inhibitor Cardiotoxicity: Contributing Factors, Appropriate Treatments, and Retreatment Options

CMEO Snack Transcript

Kerry Reynolds, MD:

Hello, I am Dr. Kerry Reynolds. And on behalf of CME Outfitters, I'd like to welcome you to today's educational activity. It's entitled *Immune Checkpoint Inhibitor Cardiotoxicity: Contributing Factors, Appropriate Treatments and Retreatment Options*. This has been funded by an educational grant from Bristol Myers Squibb.

My name is Dr. Reynolds, I'm an oncologist at the Massachusetts General Hospital in Boston. I am the Clinical Director of Inpatient Oncology here, and I direct our severe immunotherapy complications program. It is great to be here today, and I am with my close colleague, Dr. Tom Neilan, who is a cardio oncologist here. He is a world's expert in myocarditis. He sees these patients, he does research, he co-leads one of the largest clinical trials in this space, and I'm excited to welcome him. He's the Director of our Cardio-Oncology program, as well as the Co-Director of the Cardiovascular Imaging Research Program at Massachusetts General Hospital. Welcome, Tom.

Tomas Neilan, MD, MPH, FACC:

Thanks very much, Dr. Reynolds. I'm going to use Kerry from now on because ... Just for the purposes of the audience—myself and Kerry go back decades, many years I've had the pleasure of knowing Kerry as a close friend and a trusted colleague. Thanks for inviting me on today. As Kerry mentioned, I'm the Director of the Cardio-Oncology program here at Mass General, and I have the absolute pleasure of seeing and helping Dr. Reynolds and her colleagues take care of cardiovascular disease in patients with cancer. I also Co-Direct the Cardiovascular Imaging Research program at Mass General Hospital, and I'm an Associate Professor of Medicine at Harvard Medical School. As Kerry mentioned, I split my time in that proportion of my time I'm a clinical doctor taking care of patients with cancer, and then a large proportion of my time, I'm a research physician where I focus on cardiovascular disease in cancer patients. Thank you again.

Kerry Reynolds:

Excellent. And the two of us have a few learning objectives we hope to accomplish today. One, to summarize the factors contributing to cardiotoxicity associated with immune checkpoint inhibitor [ICI] use. Two, to differentiate the risk of outcome severity in patients after they experience an immune checkpoint inhibitor related to cardiotoxicity. Three, to select appropriate treatment approaches for ICI-related cardiotoxicity. And four, to appraise the current clinical evidence for and against immune checkpoint inhibitor when it comes to re-challenge in patients across the board and those [who] experience cardiovascular adverse events after immune checkpoint inhibitor therapy.

And to start, we're going to take a couple of minutes to just provide background. So, the mechanism of action of immune checkpoint inhibitors… I am going to use a video to show the mechanism of action of these agents.

Kerry Reynolds:

Many times a day, an antigen—the small blue round circle at the top—is presented on an antigen-presenting cell by way of an MHC molecule, a major histocompatibility complex molecule. It's presented to the TCR, the T-cell receptor, on that bluish purplish cell, the T-cell, and that is signal one. But in order to get immune activation, there has to be a co-stimulatory, a second signal. That is shown in the red CD80 or CD86 binds with CD28. And then the T-cell can be off to the races. It can proliferate, secrete cytokines, and start to migrate to tissue in order to recognize that antigen. But soon, because we don't want overwhelming activation, soon there has to be a break or checkpoint on the system to be able to control that immune activation. And the checkpoint, you can see [cytotoxic T lymphocyte antigen-4] CTLA-4, it comes to the cell surface and then CTLA-4 can out-compete that co-stimulatory signal to get negative regulation as a checkpoint. Similarly, that T-cell traffics out to the periphery, but soon it expresses PD-1, programmed cell death 1. In addition, the tissue has ligands. Both of these checkpoints are negative regulators to decrease immune activation. Cancer has a way of co-opting the immune system and evading it. And so, in order to have adaptive immune system activation to recognize cancers, drugs have been developed against PD-L1, the ligand, and against PD-1 on the T-cell, and against CTLA-4. And there's a newest immune checkpoint inhibitor, LAG-3, as well.

This next slide shows us the progress that has been made over the last decade. The boxes are too small to read, but they all indicate individual [U.S. Food and Drug Administration] FDA-approved indications for immune checkpoint inhibitor in the treatment of cancer. And it all started in 2011 with ipilimumab against anti-CTLA-4 in metastatic melanoma. It was in 2014 when the anti-PD-1 agents came on the scene for metastatic melanoma. And since that time, we have over 80 FDA-approved indications. And you can see, what these little boxes show is that the light blue is monotherapy, when it was just one immune checkpoint inhibitor approved for treatment, but the dark blue boxes show combination therapy. That might be an immune checkpoint inhibitor with another immune checkpoint inhibitor, an immune checkpoint inhibitor with a chemotherapy, or an immune checkpoint inhibitor with a targeted therapy. And it is clear that more combinations have been approved in recent years.

In addition, it's important because these red boxes that outline the individual FDA approvals, those are for those that were in the adjuvant or the neoadjuvant setting. It is clear more recent approvals in the earlier phases of disease, and we are treating an increasing number of patients. When we use these agents, there are side effects, immune-related adverse events, that we'll dive deep into in the talk today. But there are immune-related adverse event management guidelines that I wanted to highlight right off the bat. There are four sets of guidelines, some are hot off the press.

For example, [European Society for Medical Oncology] ESMO was just October 2022. And these provide a great structure for how to work up and treat immune-related adverse events. However, what Tom and I find is there's several gray areas, and so working together with a subspecialist can be critical when we're thinking about these conditions. And it really goes back to the fact that if we disrupt the homeostatic mechanisms, we can induce this unique spectrum of events across these organ systems. As you can see in the figure here over to the left, it's really from head-to-toe when we think about the organ systems that can be involved. And about 5-6 years ago, we were starting to notice an increased number in the patients that we were seeing with novel toxicity related to these drugs. And we have seen across the board, it can be the nervous system, whether that's the central nervous system or the peripheral. It can be the thyroid, and all of the endocrine organs. It can be pneumonitis, it can be colitis, can be joints or skin. Most common for the immune-related adverse events are actually skin, so the dermatitis, followed by the colitis and the transaminitis or hepatitis, and the endocrinopathies.

Kerry Reynolds:

You might wonder how often do these events occur? And there's a good meta-analysis of about 35 clinical trials, which shows us that these events can occur anywhere from 70% to 90% of the time, but most of them are very low-grade events, these drugs are well-tolerated, and these patients can be treated in the outpatient setting. However, a subset are higher grade or more severe immune-related adverse events. And those we think of as grade 3 and 4. That can happen anywhere from about 14% of the time with PD-1, about 30% of the time with CTLA-4 as a single agent, and if we start combining the two checkpoints, that can be over 50% of patients.

Importantly, in one of the ones that we're going to talk about today, the most fatal immune-related adverse events are those in the neurological system that have severe immune-related adverse events and myocarditis. And if untreated, if it starts to develop into a more moderate toxicity and it's untreated, they can progress to significant morbidity and even mortality. Fatality only happens about 1% of the time, but it is very important to recognize.

There's very little evidence-based for treatment. We do have the guidelines, which are largely expert consensus that I referred to before, and those can be very helpful. In general, it's temporarily or permanently stopping the immune checkpoint inhibitor. And for a large group of the toxicities, non-endocrine toxicities, we think about corticosteroids. And if that is not working, we go on to second-line immunosuppression.

But Tom, can you go over what is the incidence of ICI-related myocarditis, and what are the potential mechanisms or what's driving this type of toxicity?

Tomas Neilan:

I'm happy to, Kerry. I'm going to take a little bit of a step back, though, and reference one of your prior slides where you give a nice overview of the immune-related adverse events. And because of the recognition that a) the mechanisms which drive immune-related adverse events are likely shared across a lot of toxicities, and b) a lot of these patients have overlapping toxicities, so they'll present with both skin trouble and hepatitis, institutions like Mass General have created these severe immunotherapy complication services which Kerry leads, and it's housed principally in the oncology department. The importance of that program is that these patients get admitted and they have a centralized resource, whereby they're admitted to a service who understand these toxicities. And then that service is led by, principally, oncologists. And then, when they recognize which organ is primarily involved, they'll reach out to the pulmonologist, the hepatologist, the GI doctor, to ask for their input into the management of the patient.

Tomas Neilan:

Those centralized treatment for these patients have become critical, and I think provides real value and is the path forward. The beauty of that centralization of those resources is that, also, we need to better understand these toxicities, which we'll get into in the next couple of slides. And so, if these patients are centralized, you have a group of experts who can help drive their care to the best possible outcomes. But also, these patients can help contribute scientifically, it's remarkable when you look at these patients. They're so gracious, they've gone through so much, cancer diagnosis, sometimes failing X lines of therapy, and then they get on an immune therapy and there's a lot of excitement, and then immune therapy sadly, in some, may cause a toxicity which drives them into the hospital, yet they still remain active and engaged, and they want to help us to better understand this. I know, Kerry, you've gone through this a few times with many of your patients. And to me, it just continually blows me away about how they remain ... They just want to contribute to help us better understand.

I'm going to talk in the next few slides about the incidence of myocarditis. I'm going to try and talk about the mechanisms that drive myocarditis, and I'm going to say try because we truly do not understand. What about the incidence? Well, there are a couple of studies that help guide us about the incidence of myocarditis. To take a little bit of a step back, it was pretty much an unknown entity until one of the first publications, it was a case report New England Journal in 2016 or so, which described a few cases of myocarditis related to immune checkpoint inhibitors. They queried a pharmacovigilance database, and they found a rate of myocarditis of 0.06% with single agent therapy, and 0.27% for combination therapy. But there have been subsequent studies since which have suggested that the rate is likely higher, and these studies have varied between retrospective series and prospective series.

But I think the best data for the incidence of myocarditis comes from a recent New England Journal paper. Whereas you mentioned the group were using combination immune therapy with a traditional established therapy, nivolumab, and combining that with a LAG-3 inhibitor. And what they did in that study, which was relatively unique, is that they had a protocol-driven check of EKGs and biomarkers at established time points up to about 12 weeks. And what they found in that study is that they had an incidence of myocarditis with single agent immune therapy nivolumab of 0.6%, and with combination therapy with the LAG-3 inhibitor of 1.7%. And so, I think that gives us the best data to guide incidence, but I think even that is likely an underestimation of the true incidence of myocarditis. And I'm going to explain in a slide as to why I think that is. And on this slide is a New England Journal paper on the left, which shows the incidence 0.6% and 1.7%. But on the right is a study from Dr. Saad Mahmood in the Journal of American College of Cardiology where they looked at, when do these patients present? And the median time to presentation is about 30 to 40 days-ish, but roughly about a quarter of patients will present after that 12-week time period, or after three months.

Tomas Neilan:

And so, then, I think the incidence with single agent therapy is probably not 0.6% because you missed the tail of patients who present, so it's probably somewhere between 0.6% and 1%, and with combination with the LAG-3 inhibitors, probably 1.7% to 2%. And as for the mechanisms, which was the second question, we're entirely unclear, but there are groups who are really working hard on this, groups such as our own and other groups have published in this space. And up to relatively recently, we were hampered by the lack of robust mouse models in this space. And indeed, Dr. Jim Allison, himself, led a research group to create a robust mouse model so we can better understand the mechanisms that drive cardiotoxicity. But until then, we think about things like, are there shared antigens across the tumor, across the muscle cells, across the cardiomyocytes? There was a nice paper from Dr. Axelrod looking at alpha-myosin and whether autoantigens against alpha-myosin drive this. But these are all interesting theories and need further work. Kerry, I'm going to turn it over to you for the next couple of slides.

Kerry Reynolds:

Yeah, I couldn't agree more, Tom, that there's so much to learn and our patients are really in it with us as we wage these new waters. For the next couple slides, let's try to go through just a typical patient we might see, a consult if you will. I just put a few demographics up here and a little medical history to get us started, but I think these are the questions that we see on a regular basis. This is a 70-year-old male. For past medical history, the patient has type two diabetes, well-controlled, and hypertension, and unfortunately developed metastatic non-small cell lung cancer. And so treated with a PD-1 and a platinum doublet for chemotherapy, started October 1, 2022, so that was cycle one. Then cycle 2, 10/22, and now is coming into clinic with significant fatigue, really profound fatigue. Then Tom, at baseline, when we see these patients before they're going on immune checkpoint inhibitor, should a cardio-oncology assessment be recommended, or certain tests be recommended?

Tomas Neilan:

It's a great question, Kerry. And I think I feel pretty strongly that every patient should have a baseline EKG and a troponin prior to starting immune checkpoint inhibitor therapy. And I feel strongly that we should do that, not that we should base whether to give those individuals immune checkpoint inhibitor on the results of those two tests, but it's for patients such as the individual you presented earlier, who comes in with very vague symptoms. It is of tremendous value to have that baseline value in case you repeat that testing in the setting of nonspecific symptoms and you want to know whether there's a real change. And if I may take that a little bit further, why that's important. Often in a 70-year-old male with diabetes and hypertension, when you check a serum troponin, it'll be detectable, it'll be elevated, to use that term. But the correct term is probably it'll be detectable. Usually, it's detectable in a low range, but it'll be detectable. What do you do with that value if you don't have a baseline to compare it to? Whereas if you have a baseline to compare it to and there's not that much of a difference between those two values, you can reassure your oncology colleagues that this fatigue is not a manifestation of myocarditis related to immune checkpoint inhibitor therapy.

Kerry Reynolds:

That makes a lot of sense. And we feel so strongly about it that at our own institution, we actually have a pre-treatment lab panel that was put together and agreed upon by our severe immunotherapy complication experts. And it does include that EKG and troponin, it includes basic chemistries, LFTs, as well as a CBC. It includes a TSH and a T4, a UA to check for proteinuria at baseline, as well as hepatitis B serologies and T-spot in case we need later lines of immunosuppression down the line. Let's just take that ... I think you really actually already covered it, but if there is that 71-year-old gentleman, he comes in and his troponin is, say, 1.5 times the upper limit of normal, what do you do?

Tomas Neilan:

Well, if you don't have a baseline you're stuck.

Kerry Reynolds:

Oh, I meant at baseline. At baseline.

Tomas Neilan:

Oh, a great question.

Kerry Reynolds:

It's a little high. You're in oncology clinic, you used this pretreatment panel, and all of a sudden it's a bit high.

Tomas Neilan:

Yes, I would say, "Thank you, ma'am," and move on. And we do absolutely nothing with that value, except store it away, and use it should they present with non-specific symptoms or even potential cardiovascular symptoms later on. And so, we never act upon those baseline assessments. Now, if the baseline assessments are egregiously abnormal, then sure. If the EKG shows complete heart block or new bundle branch block or the serum troponin is severalfold higher than baseline than one would expect, then sure, that triggers that there may be something else going on and it's probably in the patient's best interest to investigate. But that's not been our experience. Our experience has been dramatically different, in that I can't think of any cases whereby, and we do this now extremely frequently, I can't think of any cases whereby we stopped the patient from having immune therapy because their troponin was X, or their EKG showed Y.

Kerry Reynolds:

Yeah. No, you're so right. And I remember a patient that we shared together that the troponin at baseline was 5, so low. And the patient had a clinical syndrome and a troponin that was over five times normal, the baseline of normal at 5, and ended up going on to have myocarditis. And that is a troponin level that we might not have thought that much of, so it's all about the delta there.

Tomas Neilan:

It's all about the change. Yeah, couldn't agree more.

Kerry Reynolds:

And is there any role in surveillance? Okay, so you have this troponin and EKG at baseline, do you follow these things throughout, or are there any specific patient populations you think about that in?

Tomas Neilan:

Oh, this is one of those questions Kerry, that I wish my internet would cut out because it's tough to know what to say. I missed one point as well on the baseline surveillance, and here I'm trying to buy myself some time while I think of an answer. And you asked about echocardiography, should we do echocardiography at baseline? We don't do any echocardiography at baseline in patients prior to immune therapy. They're very different to patients who get anthracyclines and where a baseline characterization of ejection fraction is recommended, we don't do that here because a lot of the patients who present with myocarditis actually present with a preserved ejection fraction.

And so, then, on-treatment surveillance, do you routinely do EKGs and troponins in patients who are on immune therapy, who are free of concerning symptoms? And in general, we do not. And I think most institutions do not. There are some studies where they've done this. And so, there's a nice study out of a group at Stanford, led by Dr. Waliany. They took over 200 individuals going through immune checkpoint inhibitor therapy and serially did EKGs and troponins. And in those individuals, they had a rate of over 10% of newly positive troponins and about 1.4% turned out to have myocarditis, roughly 10 times higher false positive rate than the myocarditis rate. That leads to a lot of questions, a lot of anxiety, a lot of workup. And when I spoke to these investigators, they were answering pages all the time about detectable troponins and mildly abnormal EKGs. And so, at the moment, we do not recommend doing routine on-treatment surveillance among patients who are doing fine, like the vast majority do on immunotherapy.

Kerry Reynolds:

Great, okay. Let's go back to our patient with fatigue. First of all, coming into oncology clinic after checkpoint inhibitor therapy with fatigue, the differential is quite broad. We have to go back to that figure where we think from head to toe, but it can really be hypophysitis, so one of the endocrinopathies. We think about checking that access, we think about thyroid, we think about diabetes, we think about hepatitis or nephritis. We even think about myositis in patients that are coming in incredibly fatigued, as well as myocarditis is on the list. In thinking about the workup for this individual patient that came in, the patient had normal chemistries, the patient had a slightly elevated AST and ALT, and then the patient had a CK of over 3000 and a troponin of over 1000. What would your concern for myocarditis be in a patient like that?

Tomas Neilan:

It would be very high, Kerry, to give a succinct answer. They already have evidence of likely myositis with a CK of over 3000, so they have one other immune-related adverse event. They have a high-sensitivity troponin that's severalfold higher than the threshold. They have a new symptom of fatigue, which is not an uncommon presentation. And so, my pre-test probability for the diagnosis of myocarditis here with an overlap with myositis is very high. And so, then, the next reasonable question is, "Well, what do you do next?"

We do an EKG, that's a standard test widely available. What do we look for in the EKG? We look for a couple of things in that EKG. We look for the presence of conduction system disease, because a lot of these patients will present with either second-degree or third-degree heart block or new bundle branch block, etc. We also look at some quantitative measures on the EKG, and Dr. Zlotoff published a nice paper back about two years ago, where he looked at quantitative measures to QRS duration and QTC interval. And the QRS duration looks like it increases with the development of myocarditis.

Then, the next thing we'll say is, "We need an echocardiogram." First-line test when there's a suspicion of myocarditis. And what information do we ask for in the echocardiogram? And we ask for the presence of pericardial effusions, because sometimes you see pericarditis and myocarditis coexist. We ask what the ejection fraction is, we ask whether there's localized wall thickening to suggest edema, we ask if there's regional wall motion abnormalities. And then sometimes, in some centers, we have this technique called global longitudinal strain, which is a more sensitive marker of LV systolic function. We'll ask about that global longitudinal strain because in myocarditis, it should be reduced. And then once we do that, then the next branch is, "Well, how sick is the patient?"

If the patient is very sick, we sometimes go to an endomyocardial biopsy. We do that because it's the quickest answer to the critical question. If the patient is not so unwell and doing okay, then we'll often go to cardiac MRI. But we have to be a little careful on cardiac MRI in that we ask all the same questions we asked about an echo, but we do this tissue characterization looking for edema and fibrosis or evidence of myocarditis. And you just have to be a little careful how you interpret that because sometimes the MRIs can be negative in patients with biopsy-proven myocarditis. Even individuals with negative MRIs, we'll often ask for a biopsy, we biopsy to be definitive.

And so that's our general approach. A common question I get, Kerry, is should we exclude ... You have a patient presenting with a troponin of 1000 and fatigue, should we exclude acute ...and he's a 70-year-old male with hypertension and diabetes, should we exclude an acute coronary syndrome? And my general approach to that is number 1, 2, 3, and 4 in a differential here are myocarditis. But yes, you should consider an acute coronary syndrome. And yes, you should exclude an acute coronary syndrome if the presentation is consistent with an acute coronary syndrome. And so, sometimes we'll do that, we'll either use a cardiac CT or if they're going for biopsy, we'll do a coronary angiogram at the same time. And so, that's our general workup approach to these patients.

Kerry Reynolds:

Yeah, it makes a lot of sense. And our suspicion is really high because you already referred to the timing before, but it was just after two cycles in this gentleman and then that CK, that overlap syndrome that you described. And it's interesting with the AST and ALT because that can just be in the setting of myositis. Sometimes we draw a GGT just to see, is that really coming from the liver or is that actually all muscle?

And so, can you tell us a little about the major adverse cardiac events and what we're looking out for in patients that are diagnosed with myocarditis?

Tomas Neilan:

To give us a little bit of context, it's a good question, Kerry. In patients who present with myocarditis unrelated to immune checkpoint inhibitor therapy, we see a very low rate of major adverse cardiac events and a very low cardiovascular mortality rate. If it even occurred in 2%, that would be a lot. But in myocarditis related to immune checkpoint inhibitor, we see a case fatality rate which approaches 30% and 40% in some series. And beyond fatality alone, we see a lot of adverse events, adverse cardiovascular events, including complete heart block, cardiogenic shock, ventricular tachycardia, and cardiac arrest. And so, when you lump that all together, cardiovascular mortality and major adverse cardiac events, we see a rate which is well over 50%. And that's phenomenally high, a rate of major adverse cardiac events of over 50%.

Kerry Reynolds:

Yeah, that's helpful. Does it matter, so for example, the consultation that we had had a troponin of over 1000, does the level of troponin matter?

Tomas Neilan:

We think it does. We think that the higher levels of troponin ... The challenge with these data, Kerry, are that there are so many different troponin assays, troponin I, troponin T, conventional high sensitivity, that it's very difficult to find the large dataset which has a homogeneous measure of troponin. But in general, we do think that higher troponin levels, both at presentation and peak troponin levels, and even the delta troponin, are all associated with worse outcomes.

Kerry Reynolds:

And do you notice at all that it varies by, say, the class of drug, meaning PD-1 versus PD-L1 versus combination, or about the same when you're seeing myocarditis?

Tomas Neilan:

We think the incidence is higher with combination therapy. We don't have enough data because as you know, only 10% get combination, roughly. And so, we don't know yet whether the rates of major adverse cardiac events are higher with combination therapy, except in those who get CTLA-4 therapy. We think folks with CTLA-4 therapy generally do worse, but the data sets are all inhomogeneous, and so it's tough to answer that directly like they can do for pneumonitis, hepatitis etc., because with those you're dealing with cohorts of thousands of patients, whereas here we're dealing with far smaller cohort size.

Kerry Reynolds:

Yeah, but across the board, even in our own experience, we've seen PD-1 single agent be a very significant myocarditis similar to the combo. It seems like once they have it, it really doesn't matter which class of drugs you received.

Tomas Neilan:

I think so. The good news is that we're gathering more data, and we'll be in a better position to answer that question as we gather some more data. Because it's an important thing that we get asked a lot.

Kerry Reynolds:

Yeah, exactly. And it's so important, in all of that data and actually even in clinical care, that we're truly defining myocarditis the same across all of these cohorts. Can you talk a little bit more about the definition of myocarditis in the literature?

Tomas Neilan:

Yeah. We've been trying to work together as a community to come up with firmer definitions. And with firmer definitions, you can get a very good grasp of what the incidence is and start to work towards approaches to these patients. And so, different groups have different approaches. And one of the approaches was defining definite myocarditis, probable myocarditis, or possible myocarditis; basing it on pathology, MRI, echocardiography, etc. And there's been a little bit of variability in how people think about those two things. There's a recent ICAS presentation which was a consensus for the diagnosis of immune checkpoint inhibitor myocarditis. I think they really simplified it, and they said, "Listen, there's two ways of getting at this diagnosis. Step back a little bit from the definite, probable, and possible, and say, 'This is how you get diagnosed as myocarditis and these are the criteria you need.'" And so, the criteria they said is, if you've got pathology, you've got a diagnosis of myocarditis.

Tomas Neilan:

If you do an endomyocardial biopsy and there are features of myocarditis on the endomyocardial biopsy, you have your diagnosis. If you don't have pathological diagnosis on endomyocardial biopsy, then you go to a clinical pathway, which is, your troponin is up. And then you combine that with your other testing, which is cardiac MRI, the clinical syndrome, so overlap with myositis or hepatitis etc., arrhythmias or conduction system disease, cardiac function on echocardiography, a suggestive cardiac MRI because sometimes the MRI is in between. Or even suggestive cardiac pathology on the biopsy because also sometimes as early, the myocardial biopsy is also non-committal or indeterminate. You put all that together and you say, “Yes, you have myocarditis,” or “No, you do not have myocarditis.”

And I think just to take a step back, that'll all get refined. That was the first iteration at that, we will continue to add in real-world settings, groups are going to do sensitivity and specificity, they examine how accurate they are. And I think we're going to end up refining that as the years develop into higher sensitivity and higher specificity. My sense is, the sensitivity is very high with that approach, but the specificity mightn't be as high. And so, we just need to add things to improve that specificity.

Kerry Reynolds:

That makes sense. And can you simplify that a little bit for people on the ground?

Tomas Neilan:

Yeah. Groups have tried to do that, to make it very straightforward. And there is a group out of University of Michigan who have a paper in press at JACC: CardioOncology who they've said, "Listen, we're going to take a different approach,” which is we have a simplified myocarditis approach where patients receiving immune checkpoint inhibitor presenting with symptoms and an abnormal troponin. And if it's early, so if the time is early, they have an abnormal CPK, they have an elevated, stably elevated, or a rising troponin, then it's a high likelihood of ICI myocarditis, and you rule out acute coronary syndrome, you start immunosuppression, and you complete the workup. Or, if the time from immune checkpoint inhibitor is long, so a couple of months out, their CPK is normal, their troponin is actually settling on its own, then it's a very low likelihood, and you can consider other causes of myocardial injury. That's a very simplified and very practical approach, very simplified and practical approach.

Kerry Reynolds:

And the trick is not to get so simplified because the treatments actually do have profound effect. And that's very helpful to have that streamlined approach, it's just so critical that we do have a lot of confidence in our definition because the treatments have their own side effects.

Can you walk through us a little bit about the treatments that you use for myocarditis? When do you use them, how much do you use them, and even how do you taper after that first initial pulse?

Tomas Neilan:

As an approach, Kerry, to these patients, every patient gets admitted. And they have to get admitted to a facility which can both complete the evaluation and manage the complications. Typically, we hold immune checkpoint inhibitor therapy, and that's not such a big deal acutely, as you know, because they get these therapies every two or three weeks. We hold immune checkpoint inhibitor therapy. We do our evaluation, we make a diagnosis. It's multidisciplinary: we involve their outpatient cardiologist if they have one, but outpatient oncologist, inpatient oncology team, the other team members of the severe immunotherapy complications group. And then the next question is you made the diagnosis, do you start immunosuppression? And first-line for immunosuppression are always corticosteroids. And the corticosteroids, as you know, are recommended in all the guidelines. Every guideline says start corticosteroids. What they might debate a little bit is the dose of corticosteroids. The ASCO guidelines say 1-2 mg/kg of prednisone and escalate if needed. Some other guidelines say you got to come in a lot heavier with a gram of Solu-Medrol from the start.

And these are important decisions about starting immunosuppression, because we now clearly understand that there's a link between high-dose immunosuppression like we use, and bad outcomes from a cancer perspective. But we also understand that there's a link between high doses of corticosteroids and reducing major adverse cardiac events. And so, it looks like the earlier start corticosteroids with the higher dose is associated with lower rates of major adverse cardiac events. But these doses of corticosteroids really impact cancer outcomes, as you know better than I do. And so, we may be winning the battle, but losing the war. And there's another couple of issues with these high doses of corticosteroids. The rates of major adverse cardiac events remain high. Even though we're using very high doses of corticosteroids, many of these patients are still having major adverse cardiac events. And rates of major adverse cardiac events, as shown in the slide, despite the increasing doses of corticosteroid use, have reduced a little bit but haven't actually come down to where we'd like them. There's still a lot of breakthrough cases despite these high doses of corticosteroids. And as I mentioned earlier or touched on briefly, we do worry a lot about what these doses of corticosteroids do to cancer outcomes, and I think the data suggests that it adversely impacts cancer outcomes.

Kerry Reynolds:

Really helpful, Tom. And there are those cases that do incredibly well with steroids and the troponin comes down nicely, but can you walk us through the algorithmic approach or how you think about those patients where the troponin doesn't come down like you want it to?

Tomas Neilan:

These refractory cases are common, as you've discussed, and very difficult to manage. And so typically, our approach ... There are multiple different potential approaches, but generally our approach, Kerry, is that you start corticosteroids. If the patient responds, then they transition from intravenous corticosteroids to oral corticosteroids. You make sure they remain responsive, and then they transition to outpatient cardiology follow up whereby we taper corticosteroids, usually on a weekly basis with close monitoring of their troponin and EKG. But let's say the patient, as you presented, does not respond and they're doing worse, how do you escalate care? And I don't think we really know the answer to that question. I think if you poll institutions, you'll find very different approaches.

Tomas Neilan:

In general, what we do here is, if they're getting worse, if they're hemodynamically, profoundly unwell, we consider one of three agents. We consider IVIG, consider ATG (anti-thymocyte globulin), we consider abatacept, and then there are some case reports about the use of alemtuzumab. If the patient is getting worse but they're actually not doing that badly, so let's say it's the troponin that's rising and you're just worried about the troponins rising, they're not responding, usually we add CellCept to those individuals as an additional immunosuppression. We have two approaches. One, patient is doing okay but you're not happy that the immunosuppression is doing its job, we add CellCept. On the other side, patient is not doing okay and we need acute immunosuppression in addition to the corticosteroids, then those are the options, the abatacept, alemtuzumab, ATG, IVIG. Some institutions talk about plasmapheresis, but not a lot of institutions are doing that now. And so, those are usually the things we think about.

But I think we need more data, Kerry, to better understand what the best thing to do is. We all have our anecdotes. And so here, I'm showing one of our anecdotes, one of these refractory cases where a patient was admitted to an institution, it was a melanoma combination immune checkpoint inhibitor therapy, cardiovascular symptoms, new right bundle branch block, gets admitted, gets diagnosed very quickly by the institution, gets on CellCept 500 mg twice daily, also gets on a gram of Solu-Medrol at the same time because that was what the institutional practice was. Troponin continues to rise, the patient develops complete heart block, ventricular tachycardia, cardiogenic shock, gets admitted to their intensive care unit, and they're rounding on this patient, not entirely sure what the next steps were. And one of the residents tells the team, "Listen, I read this case report about the use of abatacept in a patient. Can we give this individual abatacept?"

And they give this patient abatacept, and they had this remarkable decline here shown in blue, in their serum troponin, and after a couple of days, they were off all the vasoactive agents and back in sinus rhythm. But we all have these anecdotes, and we're not entirely sure whether these anecdotes translate into the same response using a rigorous approach. And so, what we need is, we need rigorous data. And I am delighted to be working with you on trying to find some rigorous data in this setting. And so, what I'm talking about is a study that we're doing together with Dr. Reynolds and other team members throughout the United States and Canada, where just under 400 individuals with immune checkpoint inhibitor myocarditis will get randomized to usual care, which is corticosteroids, or usual care plus abatacept, and that's the ATRIUM trial. And so, in that ATRIUM trial, we're going to look at whether corticosteroids plus abatacept is associated with better cardiovascular outcomes. And that will give us the real-world, the rigorous data we need to advance the field.

Kerry Reynolds:

Yeah. And when we talk about these treatments too, so often, sometimes that myocarditis does overlap with that elevated CK in myositis. And so, we think that in those types of patients, we really have to look for weakness and we involve our neurological colleagues right off the bat because there can also be an overlap with potential myasthenia gravis. We ask those patients, "Do you have any diplopia? Do you have any dysarthria. Swallowing wise, do you have any dysphagia?" Is the voice abnormal for dysarthria or shortness of breath, meaning, there is the phrenic nerve that goes to the diaphragm, and sometimes that can be an early sign of myasthenia gravis, when patients are just short of breath. We really go through that weakness approach, making sure we often think about what is their respiratory function, their negative inspiratory force? Our respiratory therapists help us. We think about getting an EMG on some of these patients, because sometimes we have to co-manage that myocarditis, even though it might be refractory, also with a severe myositis or even that overlap with myasthenia. And sometimes we're using IVIG for that alone. And even in this trial in ATRIUM, you're allowing IVIG because that overlap syndrome can exist. But the right answer and how we navigate this, just like you said, really needs more evidence base to it.

Tomas Neilan:

Completely agree, we need rigorous data, otherwise we'll be having this conversation in a couple of years' time thinking that the algorithm should be X, Y and Z. And there's clearly equipoise out there, and when there's equipoise, then there is need for this rigorous approach to better understand whether this combination, upfront immunosuppression is associated with better patient outcomes.

Kerry Reynolds:

Exactly. Okay, so let's switch gears, let's go to a different type of consult. This is consult number two. This is a 55-year-old gentleman. No past medical history, a healthy lad, as you would say. He was diagnosed with metastatic melanoma and unfortunately, he's BRAF wild type, so he doesn't have a BRAF mutation available for targeted therapy, and also had brain metastasis. Standard of care is combination IPI-NIVO, so that dual checkpoint inhibitor, both the CTLA-4 and PD-1. The patient had two cycles, and already there was evidence of response. Unfortunately, the patient did develop a myocarditis and myositis, but did well. And that's a key part I think, to also point out, is that we do have patients that do well. And he was able to taper with steroids off at about less than eight weeks or so, so off after two months. Then because of his response, he actually was just followed, making sure that he did okay with those immune-related adverse events and continually checking his cancer with scans.

Kerry Reynolds:

But six months later is when he popped up with progression of his cancer. What do we do at a time like that? And often, I think it's hard in these patients because we definitely need more evidence in this space of who do we challenge, when do we challenge, and how will they do? The evidence that we do have for ICI re-challenge is from a variety of different studies. There was a Vigibase study which is the WHO: it's self-reported though - it's either patients or providers or pharma companies, so there's incomplete information. But in that database, they had 452 cases, not all of myocarditis at all but they had 452 cases with ICI re-challenge, and about 30% of the patients recurred with an initial immune-related adverse event. Now, we don't know in something like that information to know, did they get a different type of immune-related adverse event that was not recorded? But at least what we do know from a study like this, is about 30% recurred with that initial immune-related adverse event. They found that colitis, hepatitis, and pneumonitis had higher rates of recurrence, whereas adrenal rates were a little bit lower, but that's probably because the patients just stayed on the long-term adrenal replacement with corticosteroids.

In other studies, as you can see here, there were, say, 40 patients re-challenged and about 43% had a recurrent immune-related adverse event, about 13% did have a new immune-related adverse event. They looked at this in cohorts of lung cancer, renal cancer, melanoma. A lot of this, so far, has been pretty much single institution data, a lot of retrospective data. But what we can say is roughly about 30% to 50% recur with immune-related adverse event. And there might be a signal that if it's an early immune-related adverse event, there's a bit of a higher risk of recurrence. And if it's a more severe grade immune-related adverse event initially, it is potentially that it's a higher risk of recurrence. And so, most of this is not in the field of myocarditis, because myocarditis is one of those events where you talked about the higher fatality rate. And so, as you think through somebody like this where they had two checkpoints, they are responding, they did respond to the two checkpoints but got this serious toxicity that really recovered quite fast, and now you're months later, how do you think through that? And is there any data about re-challenging a patient like that, or is there any even case-by-case assessment that you would think about?

Tomas Neilan:

The easy answer here, Kerry, is to say nope, you do not re-challenge a patient. But that's the easy answer. I think there are some data to help us guide who can be safely re-challenged. And the short answer is yes, some patients can be re-challenged, I think, but the majority of patients cannot. And so, what data can we use to guide us as to whether we can start the conversation about re-challenge? There's a nice study from a group down at MD Anderson, Dr. Nicolas Palaskas, who looked at endomyocardial biopsy, so taking samples from the heart and using that data to say, "If there's low grade inflammation, can we continue a re-challenge with immunotherapy?"

Tomas Neilan:

And the answer was yes, small sample size though. And all of these are small sample size. Lower grades of inflammation on the heart, patient could be continued on therapy or safely re-challenged. I think that's one approach. Another approach is, how severe was their initial presentation with myocarditis? If it was on the more severe spectrum, then that patient cannot be re-challenged. If the initial presentation was with combination immune therapy and you're thinking of re-challenge with single agent, then that's a conversation you could have. Is the patient off immunosuppression? Because they have to be off immunosuppression. Can they undergo surveillance if you do re-challenge them? And so, these are all the questions you go through with their outpatient provider and the patient themselves, with the understanding it's easy to say no, it's far more difficult to say yes. But there probably are a very small subset of individuals who can undergo re-challenge.

Kerry Reynolds:

Yeah, it's incredibly helpful as we learn more about these case presentations. Consult three. This will be our last consult for the day Dr. Neilan, but we have a 72-year-old female. This patient has hypertension, hyperlipidemia, and diabetes, was diagnosed with metastatic melanoma, and was on PD-1 monotherapy. Developed an immune-related adverse event, hypothyroidism, an endocrinopathy for which we replace the thyroid hormone, and had a complete response. The question becomes then, when do you consider immune checkpoint inhibitor therapy and stopping that therapy? Many of the clinical trials to date with some of the PD-1 agents have showed that you can stop at about two years. Can you stop less? Should you continue some patients longer? This is really an area that is being hotly investigated, and it's going to be important to have an evidence base that really shows us and guides us here when to stop therapy.

I think one thing does get brought up though, is what are the toxicities that patients may be developing? Are there any chronic toxicities? And are there any long-term effects from being on immune checkpoint inhibitor? This next slide really shows us that from the CheckMate-067 data at the 6.5-year follow-up mark, it's remarkable to see these durable improved clinical outcomes with IPI-NIVO in patients with melanoma. But Tom, can you talk to us a little bit about, is there any concern that there might be longer term side effects or how do we think about managing these patients? It's really a good news story overall to see those survival curves.

Tomas Neilan:

It is indeed a good news story, Kerry. One of the things we've started to think about recently is whether there may be potentially chronic cardiovascular complications related to immune checkpoint inhibitor therapy. Now, the thing about myocarditis that we've spoken up to now, typically it's acute. There's a small tail which presents after three months, but most of the patients present early. Are there chronic cardiovascular complications that can result? And we think there probably are, but they're probably only current individuals who are susceptible to them in the first place. And so, the principle chronic cardiovascular complication we think about is accelerated atherosclerosis or progression of atherosclerosis related to these immune checkpoints. And these immune checkpoints that are being targeted for cancer are also key regulators of atherosclerosis biology.

Tomas Neilan:

And there's some studies out there where they did two things. One is they asked whether there's accelerated atherosclerosis in patients on immune checkpoint inhibitor therapy. And number two is whether the accelerated atherosclerosis translates into increased atherosclerosis-related cardiovascular events. There's a study from Dr. Zsofia Drobni in *Circulation*, which said that there was a threefold increase in atherosclerosis progression on these immune checkpoint inhibitors, and there's a lot of biological plausibility to support that. And then Dr. Drobni looked further and said, well, whether there's an increase in atherosclerotic-related cardiovascular events and found the same threefold increase in rates of MI, coronary vascularization, and ischemic stroke. We think acutely, the concern is myocarditis, but chronically, especially in patients who get adjuvant or neoadjuvant care or who are expected to live a long time, there may be an increase in atherosclerosis-related cardiovascular events.

Kerry Reynolds:

Yeah, these are going to be important to figure out as patients live longer and longer. And just to summarize, it's been a great discussion I think, we hit on a few high points that dual immune checkpoint inhibitor therapy seems to be associated with a bit greater risk of immune checkpoint inhibitor cardiotoxicity, so have a high suspicion. Two, that troponin, EKG changes, echo, and cardiac MRI may be useful in identifying myocarditis, but they do have limitations and sometimes we have to have the gold standard, cardiac biopsy. Three, for patients experiencing myocarditis, we stop the immune checkpoint inhibitor and we begin steroids, often higher dose steroids, and important to give them early. And then for those patients that need additional immunosuppression in refractory or unresponsive cases to steroids, we went over that as well. And we talked about how there's no real clear guidance for possible re-challenge after immune checkpoint inhibitor-mediated myocarditis. And we know that if we look at other studies with other immune-related adverse events, about a third to a half will recur with an immune-related adverse event after re-challenge.

Let's just go over the SMART goals. SMART goals are specific, measurable, attainable, relevant, and timely. And so, be vigilant for signs of cardiotoxicity. We have to encourage pre-therapy cardiac evaluation. And what we mean by that is really more just that baseline troponin level and EKG. Employing early and high dose immunosuppression for patients with immune checkpoint inhibitor-mediated cardiotoxicity can have important outcomes. And if re-challenging patients with immune checkpoint inhibitor therapy after an IRAE is considered, the level of suppression has to be considered, their treatment response has to be considered, and importantly, the severity of the immune-related adverse event. And we have to know that the neurological and the cardiac ones are most fatal.

And so, to receive CME and CE credit for this activity, participants must complete the post-test and evaluation online. Just click on the request credit tab to complete the process and print your certificate. It's been wonderful to have this session with you, Tom.

Tomas Neilan:

Likewise, Kerry. Absolute pleasure. And I would say it's just an absolute pleasure working with you clinically and both from a research perspective. We need better answers, these patients deserve better answers, and working together is the path forward to try and give them those better answers.

Kerry Reynolds:

And I think that's one of these key things, is that often these immune checkpoint inhibitor immune-related adverse events require a team. And so, we hope you find that team at your own institution. Thank you so much.

Tomas Neilan:

Thank you so much.

