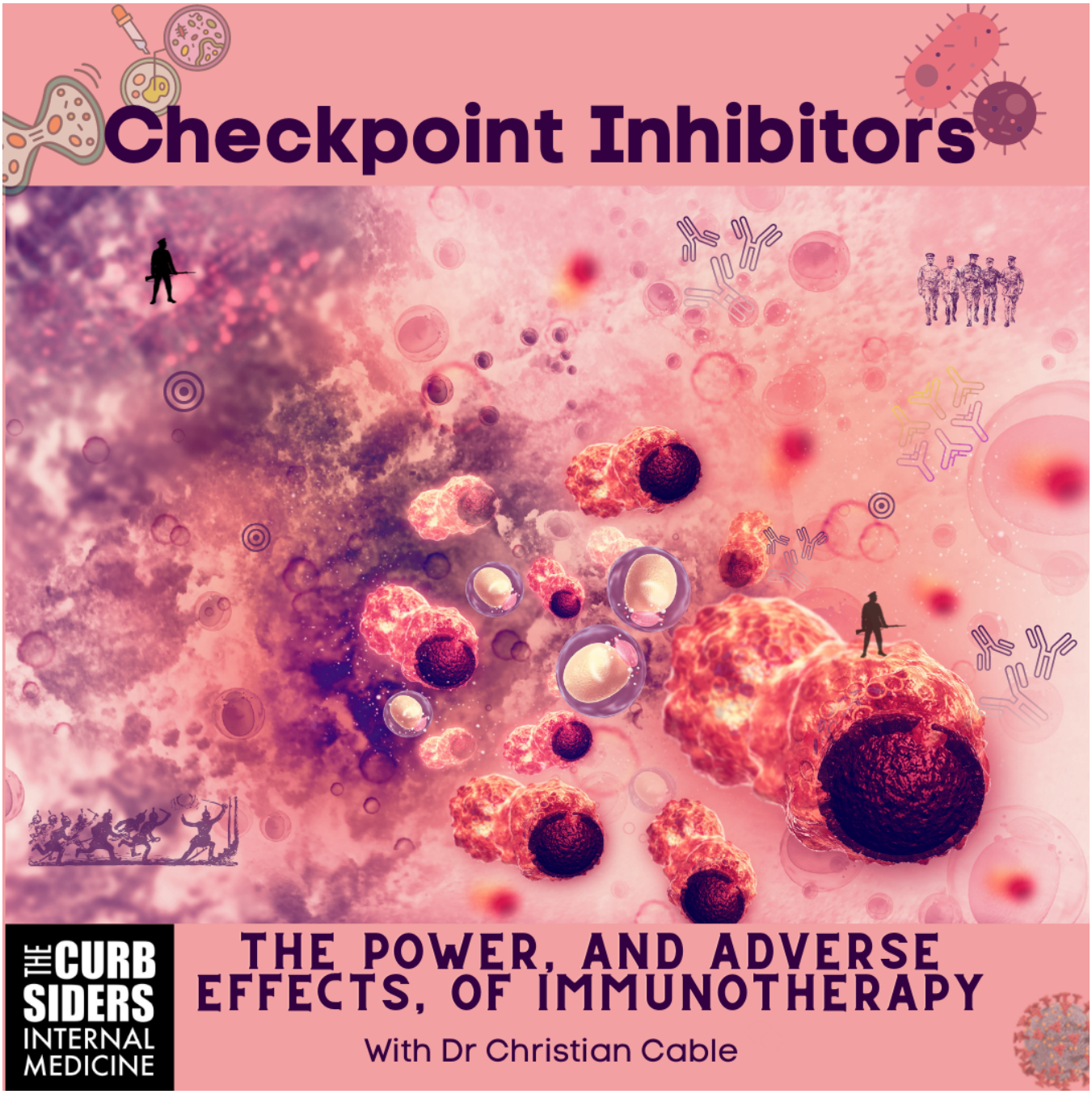
#342 Checkpoint Inhibitors:

The power, and adverse effects, of immunotherapy (ACP 2022)



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Paul: This is Paul Williams. I am here at ACP 2022 with my excellent colleagues, Dr. Nora Taranto, Dr. Molly Heublein, and Dr. Chris "The Chiu Man" Chiu, who is off mic. We had an excellent episode. Watto is elsewhere. The less said the better, but we're going to muddle through without him. But on tonight's show, we have the pleasure of talking to Dr. Christian Cable about these immune checkpoint inhibitors, and their role of medicine, and the potential things that can go wrong with them. And we'll talk more about that in a bit. But before we do that, I'm going to completely throw her off and ask Nora will tell us what exactly it is that we do here.

Nora: Sure, Paul.

[laughter]

Nora: We are The Internal Medicine Podcast. We use expert interviews to bring you clinical pearls and practice changing knowledge.

Paul: Great. And then further complicating things, why don't I ask you, Dr. Molly Heublein to tell us about our guest and a little bit about what we talked about today?

Molly: Sure. We had a fantastic conversation with our guest, Dr. Christian Cable. Dr. Cable is a hematologist/oncologist at Baylor Scott & White in Temple, Texas, where he serves as the Baylor College of Medicine Associate Dean for admissions and students. And previously served as the hematology/oncology fellowship director and GME director. He loves to learn and teach hematology and is a frequent speaker for the American College of Physicians, and serves on the 2022 and 2024 ACP scientific program committee. Christian is the Mixup 20 Hematology section editor. He and his wife, Jill are fierce double pickleball players. On this episode, we talk about pickleball-

[laughter]

Molly: -and immune checkpoint inhibitors. Dr. Cable talks to us about how these medications ramp up the immune system to try to beat cancer cells and in the meantime that can also cause other autoimmune complications, specifically, endocrine and rheumatologic side effects, and can help us-- he talks through with us how to look out for those and first steps on how to address those.

Paul: Before we get to it, anyone have any puns that they want to share with us? No, excellent, perfect, then on with the show. Christian, thank you so much for joining us on the show. We are here at ACP 2022. The astute listener may hear just spirited blues music playing in the background unless we manage to fix that in post. So, fingers crossed. I'm of course joined by Nora Taranto and Molly Heublein. Hey, guys. How are you?

Nora: Hello.

Paul: And we are of course joined by Christian, who's going to tell us all about checkpoint inhibitors. But before we get into that, Christian can give us a one liner to describe yourself.

Christian: Yes. I am a chronic nerd who loves to learn and teach.

Nora: It's amazing.

[laughter]

Molly: Short and sweet.

Paul: Can you give us one hobby that you like to do outside of learning and teaching?

Christian: Yes. I have a chainsaw named Rachel the IV and we have been clearing land behind the house.

Paul: Oh, amazing. To what end just to make it prettier or is something going to happen out there?

Christian: We're hoping to develop it into a branch for special needs adults.

Paul: Oh, incredible.

Molly: Awesome.

Nora: How much land clearing do you have to do to do that?

Christian: In Texas, it would be called a Ranchito.

Nora: Okay.

Paul: [laughs]

Christian: It's 125 acres behind our place. I find joy working on the land.

Nora: I feel I have to ask this. Was there a Rachel the III, the II, the I?

Christian: Of course.

Nora: Just making sure.

Christian: Of course.

Nora: Okay.

[crosstalk]

Christian: Rachel the III and Rachel the IV were commercial chainsaws and Rachel the III had to have a heart transplant. But she's back working as well and Rachel the IV just felled a dead tree, and we're looking for productive ways to reclaim the lumber.

Molly: Nice.

Paul: That's tremendous.

Nora: What is your favorite failure?

Paul: Oh, jeez. Right into it. All right.

Christian: Right into it.

[laughs]

Christian: I once walked 14 miles to avoid walking 13. I was ascending Pikes Peak and I got high altitude sickness, maybe even pulmonary edema at about seven miles up. Instead of making a 13-mile trip up and taking the train down, I had to turn around at seven miles and go right back. It's real when you descend, you start feeling better. But between six and seven miles in, I could only walk about 20 yards without getting dyspneic. That was a failure, but I didn't end up in the hospital. So, I guess, it was a good one.

Molly: Not a total failure.

Christian: Not a total failure.

Molly: Yes.

Christian: That's right.

Molly: We're just starting out the conference here, but are there things that you're most excited about here at ACP or things that you really love about these in-person conferences?

Christian: Molly, you're right. This is the first in-person conference I've been to in two years. I don't really mind the music in the background.

Molly: [laughs]

Christian: Maybe we can't take it out and post, but everybody is just so happy to see people. I'm going to be looking for my Hem/Onc peeps. I love hearing new things and hearing new teachers. And then I also went to the board review. I just hit my second recertification. I'm taking the easy way out and doing the longitudinal knowledge assessment. But I know more about Internal Medicine than I knew on Sunday. So, that's good.

Molly: Excellent.

Paul: All right. Well, I don't want to deprive you of the opportunity to tell us about-- Let's go favorite book unless there is another piece of culture that you'd like to share with us?

Christian: *Anna Karenina,* I'll share the opening line. It's the best part. It's like, “All happy families are alike, each unhappy family is unhappy in its own way.”

Paul: Oh, that's beautiful.

Molly: It's a beautiful book.

Nora: Yeah.

Christian: Yeah.

Paul: All right. Well, with that and me showing how uncultured I am, why don't we actually move on to a case and let's get to the meat of this talk. So, Nora, why don't you talk us through our first patient, so we can learn a little bit about?

Nora: Awesome. To start, we have Mark. Mark is a 65-year-old male with hypertension, hyperlipidemia, BPH, and a new diagnosis of metastatic melanoma. He’s mets to the liver and the lung in particular. He's established care with an oncologist already and he's actually about to start a new medication for treatment of the melanoma called nivolumab. You're his primary care doctor. He wants to discuss the medication with you prior to starting it, since he trusts your opinion and doesn't know too much about it. And so, just to take a step back for a moment, nivolumab is under the class of immunotherapy that we're hearing more and more about. What exactly is immunotherapy?

Christian: Immunotherapy, it's got a long history. The last 10 years have been fascinating. But in essence, it's trying to turn on the immune system to recognize cancer. I think that it's intuitive to recognize the immune system and its defense against infection. But a lesser-known function is to call out early cancers and it all happens behind the background, behind the scenes, you just don't know it. Immunotherapy is a way to manipulate the immune system. In our patient Mark's case, to recognize his melanoma as cancer, and to actually attack the cancer, and hopefully not the normal parts of Mark, which is that some of the mischief you can get into with checkpoint inhibitors.

But immunotherapy in general is very attractive to both patients and physicians. Because the side effects are certainly different and usually less severe than traditional chemotherapy. People don't lose

their hair, there's not severe nausea and vomiting, there's not the same susceptibility to sepsis. But in general, I think I would explain it just saying, you're trying to get the immune system to take care of the cancer, to use the body's natural defenses, to get rid of cancer even in an advanced state like our patient, Mark.

Paul: That sounds a little bit like the spiel that you give to patients about these medications. Now, let's pretend I remember some of my immunology, but not at the time.

Christian: Yeah.

Nora: [laughs]

Paul: It advances us talking to just the internist in terms of how these medications work specifically. Maybe not too, specifically, because again, I ride [crosstalk] middle distance. But broadly, what targets these go after and how do they actually function?

Christian: This is where it gets really fun, because I think we're at a time where the phenomenon is leading the pathophysiology. The honest answer of how exactly does it work is, I don't know. I think that one of the first immunotherapies was a surgeon named Coley in the 1890s. He did something. Am I allowed to say that surgeons can be crazy on this podcast.

Nora: [laughs]

Christian: I don't think an internist would have done this.

Nora: I think if they’re from the 1800s.

Christian: Yeah.

Molly: Exactly.

Paul: Also, probably not listening.

Nora: Different age.

[crosstalk]

Paul: Okay, maybe not. Let's say, if I don’t--

Christian: Coley had an idea that giving bacterial toxins and thankfully he killed the bacteria first, because it was Strep pyogenes and Serratia marcescens. He would give them to people trying to treat cancer. The first case he tried was sarcoma. He worked with Dr. Ewing. They were at the same hospital. What happened is occasionally a patient would respond and the tumor would shrink. Uniformly, people don't like getting bacterial toxins [crosstalk].

[laughter]

Christian: Everybody got sick and occasionally, somebody got better. That went on until 1963. You could buy Coley's toxins until the FDA after thalidomide started tightening down how we approved drugs in the United States. The next thing with immunotherapy, which is really cool is the radiation oncologists noticed that if you were to radiate one tumor and that's really after surgery, the second anti-cancer treatment was radiotherapy, you could radiate a tumor, and I think the case was actually melanoma in a very immune active tumor, and a metastasis would shrink. The physician that wrote up the case actually made up the word, abscopal. The abscopal effect was, I treat radiation therapy to a primary and distant from the radiation, the metastasis gets better. So, that was immunotherapy, because essentially, what you were doing was exposing new antigens, damaging the primary by radiotherapy, and stimulating the immune system to attack the met.

Paul: I just got so excited.

Nora: Very cool.

Molly: Yeah.

[laughter]

Paul: Very cool, but that's incredible.

Christian: We're all familiar with bone marrow transplant that started in the 1950s in a way as a response to how to treat radiation poisoning from World War II. The first six patients with allogeneic transplant published in the New England Journal 1957, they all died in the first one hundred days, because HLA typing wasn't discovered until 10 years later. Incredible. That was adoptive immunotherapy, where it became clear that the reason leukemias could be cured with an allogeneic transplant is that you adopted somebody else's T cells. Those T cells recognized your leukemia as foreign. So, it really was the self-non-self.

You fast forward the 1980s, there's a series of Time magazine covers the cure for cancer. One of them was interferon. I call interferon influenza in a jar. I had the misfortune as a fellow, Nora, you won't. I had the misfortune as a fellow to prescribe interferon. One of the things you had to look out for actually was depression to the point of suicide.

Paul: Yeah.

Nora: and **Molly:** Mm-hmm.

Christian: It's real. And then when I was a fellow late 90s, early 2000s, subsistence in a jar interleukin-2. That's what we used to give for melanoma. For me, seeing the melanoma story as the leading edge of immunotherapy, comparing it to giving people high dose interleukin-2, which you really

had to do in an intensive care unit with vasopressors. Everything that could go wrong did and what you were shooting for was about 5% of people would be long-term survivors. So, it's interesting how does a checkpoint inhibitor work? The first one was called CTLA-4, cytotoxic lymphocyte antigen 4 inhibitor and it is essentially inhibiting the T cell from shutting down. It keeps the T cell active. Program death, PD or program death ligand similar, they're auto control mechanisms for T cells. They're in essence keeping T cells active, but what happens after that it's like tipping off the dominoes. I think it's a Venn diagram and a black box. I don't know. Because there are now, 10, maybe 20 different types of T cells described. There's a crosstalk between T cells and B cells. This whole cell mediated versus humoral is probably too simplistic. In essence, we know that you wake up the immune system and then in a substantial number of patients across a very broad number of diseases, it does better than chemotherapy in long-term survival and in a few probably cure.

Nora: What are the common cancers that we will see these being prescribed for?

Christian: Yeah. I think the way to think about that Nora is think about what are the common cancers. Let's talk about lung, prostate, breast cancer, colorectal cancer. Lung cancer is where you're going to see it the most. Because lung cancer, it has indications now in small cell and non-small cell. With non-small cell lung cancer, we were always looking for people with so-called druggable mutations like EGFR or ROS1. They would have tyrosine kinase inhibitor pills. A broad number of patients beyond that are going to be eligible to receive a checkpoint inhibitor, usually, a PD-1 inhibitor in combination with chemotherapy. I would say lung is number one.

Prostate cancer not yet, but the research is happening. Prostate cancer, the advances have been more in ways to manipulate the hormonal system. With colon cancer and this is another interesting thing. It's colon cancers that have high microsatellite instability. And so, high MSI, which is a way to categorize colon cancer essentially shows you more antigenic variation, and that fits with the neoantigen, and recognizing that theme. And then finally with breast cancer, it's in the type of breast cancer that needed it the most and that's triple negative breast cancer. You don't have estrogen as a target, you don't have HER2/neu as a target. Triple negative has been a bad actor and that's where immunotherapies are. You'll see it less commonly, but very importantly in Hodgkin lymphoma, in non-Hodgkin lymphoma. I just say, less commonly because those are less common diseases.

But I would say that the practicing internist is going to see this in lung cancer and then let's not forget melanoma. Melanoma, there's even a categorization of non-melanoma skin cancers which don't even make the charts. And then of course, Melanoma can metastasize anywhere, any when. It's one of the ones that can metastasize 20 years after the primary, it's one of the ones that can go to the heart, the brain, anywhere. Melanoma in renal cell, which both have active indications have long been understood as immunologically active tumors. We know renal cell carcinoma, Stauffer's syndrome, it's the internus tumor. So, I think it's getting easier Nora to tell you the cancers where it's not going to be used.

Molly: That's so exciting that it's now available for our patients and such a fascinating history of how we got to this place. What does it actually look like for patients? What kind of experience do they have receiving these treatments?

Christian: Molly, it's very different than traditional chemotherapy and it's even different than more common monoclonal therapy. I grew up in the days when Rituxan was coming, rituximab was coming of age, and infusion reactions were very common. It was a murine antibody and I used to tell patients that, “Your body doesn't like Mickey Mouse running around in your veins. So, you're going to get some fevers, and chills, and the shake, and the bake.” The first is the worst. That was the spiel. We don't really have that spiel with the checkpoint inhibitors. The infusion reactions are less common. They're not emetogenic. There's no real immediate effect. It tends to be pretty anticlimactic. And so, really where we focus most of our counseling is, if it were combined with chemotherapy, which is common in lung cancer, we focus on the nausea prevention from that and all of the normal things watching for fever and what is our emergency plan.

If it's only immunotherapy, then the counseling really is okay. If you're going to wake up your immune system, what we hope happens is it recognizes the tumor, what we hope doesn't happen, but we're very much watching for it is autoimmune. With the patient, I just talk about hypothyroidism, which is a common autoimmune condition that most people understand. Then in general, I talk about inflammation. That's how I think about the side effects of the checkpoint inhibitors. The good thing we want to inflame is the cancer that can lead to long-term disease control, even cure. The bad thing I want to inflame is anything else and it can inflame almost anything else.

Nora: Just to name the different categories. So, we have PD-1 inhibitors, we have PDL-1 inhibitors, and then we’ve CTLA-4 inhibitors. What are the just couple common medications that we would hear and which class do they fit in?

Christian: To my knowledge, there's only one in the CTLA-4 inhibitors that's ipilimumab. It was one of the first and it's the only in class. The way that I came to know this medicine is we actually had a patient-- I practiced in Central Texas and our quaternary referral center would be MD Anderson. There was a patient on clinical trial with metastatic melanoma, who presented with hypophysitis to our hospital. It's a very unusual diagnosis to see somebody panhypopit and I was consulted because our team, because they were on a clinical trial. There's this letter and a number, and it wasn't even named ipilimumab yet, and I had no idea. So, that was my first exposure. And still hypophysitis up to 5% of patients with CTLA-4 inhibitors. The more common class is PD-1 or programmed death ligand-1, which I think would be a good name for a metal band.

Paul: For sure.

Nora: [laughs] So true.

Christian: Those are the same class, those are the same set of side effects, and those are much more commonly used. The paradigm would be nivolumab, pembrolizumab, and there're several others in that class as well. So, essentially, ipilimumab, nivolumab, pembrolizumab. One is a single class and the other two representing a class effect for PD-1 and PD-L1.

Paul: Exciting to have these medications, exciting to have the capacity to treat things that we hadn't been able to treat well before. But of course, we're going to spend a lot of time talking about things going south. Nora, tell us a little bit more about Mark and his course with the nivolumab.

Nora: Great. So, Mark, yeah, beautiful.

Paul: Thank you. Yeah, let's just pausing now [crosstalk]

Molly: [laughs]

Paul: Almost felt natural.

Christian: It used to be that the competency of an oncologist was to manage drugs with narrow therapeutic indices. It's not true anymore. Now, it's pronouncing the names of the meds.

Paul: Yeah. With confidence, I feel like [crosstalk] probably part of it too. Yeah, you can have the question mark like I have a [crosstalk]. So, I would make a lousy oncologist.

Nora: It doesn't matter how you actually say it.

Christian: [laughs]

Nora: It's the confidence is really key.

Paul: That's true [crosstalk].

Molly: [laughs]

Nora: Mark is reassured by your spiel about the nivolumab. He starts it and his melanoma actually responds really nicely. He, two months later comes to you with a couple of new complaints. He says that, "He can't taste food the same or really chew as well," because he feels his mouth is dry, which has not been an issue for him. He also says, "His eyes are a little more irritated than they used to be. They feel gritty and dry." So, you've already begun to talk about these immune-related adverse events or IRAEs, you'll sometimes see the acronym for. What are common autoimmune conditions that occur in patients like this like Mark and what do you think is going on?

Christian: Okay. Let's talk about Mark specifically and then we'll expand out. In a patient on immunotherapy that presents with dry mouth and dry eyes, it's a sicca syndrome and it is related to Sjogren's, but not the same. I think that's the general theme is that you can pretty much get any rheumatologic autoimmune disorder with the exception of systemic lupus that hasn't been reported. But you can get pretty much any of them. However, they're a little different. The sicca syndrome tends to be lack of saliva is more prominent than lack of tears and the autoantibodies tend to not be positive. Just other rheumatologic disorders, inflammatory arthritis, it can do a great imitation of rheumatoid arthritis

or the spondyloarthropathies. However, less likely to be seropositive to RA, CCP, less likely to be positive, HLAB-27, less likely to be positive, but the syndrome is the same.

That's the triad that I'm really excited about that we've got Dr. Cappelli, who's speaking about the rheumatologic manifestations. We've got Dr. Eck speaking about the endocrine manifestations. The endocrine manifestations are the most common. I would say the ones we have to look out for are hypothyroidism, hyperthyroidism. This is really one of the first time as an oncologist, I'm thinking about the adrenal glands. Outside of the context of I give a lot of steroids and I need to think about secondary adrenal insufficiency. So, pretty much you run through the rheumatologic syndromes and there will be a correlate with the immune checkpoint inhibitor toxicity.

There are some distinctions and differences. They tend to have less seropositivity and there're some interesting associations like myositis. Dermatomyositis is actually rare with the checkpoint inhibitors, but polymyositis can indeed happen. It's going to present the same way clinically. I've got sore muscles, I've got proximal muscle weakness, I've got high CK, it is even rhabdo level high CKs. And then the weird association, the dangerous association is it can be associated with cardiac myositis, cardiac involvement or even encephalitis.

Paul: Do these tend to segregate out cleanly? In the absence of positive serologies, do you typically see just the symptoms that are consistent with sicca and they don't have the inflammatory arthritis or can you see a mixed picture, because it's so interesting that they would mimic these rheumatologic conditions in the absence of positive serology. So, do these things really serve? This discrete in your clinical experience or is there overlap you see sometimes?

Christian: The truth is, I don't know. The truth is, I don't know. As I've read about it, it seems to be more clean than the real world of overlap disorders and there are less extraarticular problems described. So, my intuition tells me you're right. I'm not sure.

Nora: I guess with the exception of the myositis, which comes with this potential host of myasthenia, myocarditis kind of that interesting picture.

Christian: And that is, it's rare but serious.

Nora: Yeah.

Christian: It's still uncommon, but I think what I'm learning, what we're learning as consultants and as primary physicians is that these are whole new classes of side effects. I didn't like giving Adriamycin or cisplatin but the side effects were predictable. They were stereotypical. You knew what to look out for. You knew in a patient receiving cisplatin that you needed to pay attention to magnesium if their potassium was low. This is a brave new world. And so, I think what I do, well, I know what I do is ask for help.

Molly: Just good advice for everyone. [laughs] Do you tend to see these side effects early on after starting treatment or is this something that's more of a cumulative dose toxicity that you see over time?

Christian: Yeah, that's a great question. The earliest one would be dermatitis. The earliest one is going to be a rash, an inflammatory rash. Then probably after that would be hypothyroidism. But the timing tends to be three weeks to a few months. Now, the interesting thing is, even when somebody has completed a course of therapy, because not all of them are given indefinitely, it can happen years later. It's one of the ones where I keep in my progress or my problem list, patient has received immunotherapy, because it would change my pretest probability considering future autoimmune diseases. Most of the time, it's going to be within weeks to a few months. However, you can't cross it off the list even if it was two years back that they had their last dose.

Molly: And are these common enough that you're checking routine labs like say, thyroid panels every few weeks with early treatment or just monitoring symptoms?

Christian: Yes, no, you're right. That's been new for us. New in a couple ways. First of all, the endocrinologist reminds me that we tend to be diurnal and so, they like morning labs. This is new for me. I never really cared when somebody got their pre-chemo labs just get it at the most convenient place for you. At 0800, maybe 0755 if you're feeling spicy, you need to check the cortisol, you need to check both the TSH and T4, because TSH as a screen itself is insufficient, because it could be central, it could be hypophysitis. Electrolytes and a glucose, so, I can probably justify a CMP, because I also get the liver enzymes as well and hepatitis as a possible. So, the additional ones the thyroid studies, the cortisol, that's new for me checking, a CMP and a CBC are pretty routine.

Molly: Are you checking auto antibodies in anyone?

Christian: No.

Molly: Okay.

Christian: I'm not.

Molly: Okay.

Paul: [laughs]

Christian: No, because I wouldn't know what to do if I found them.

Molly: That's how I feel.

Christian: That's right.

Molly: Okay.

Christian: Yes.

Nora: [laughs]

Christian: Don't check a lab unless you have a plan for the result.

Paul: I do want to go back. I love the point about asking you for help. I would love to know exactly what that help looks like. I feel again me as a very broad thinking primary care doctor, if someone is on any therapy for cancer and then they come to me with a new symptom, I'm like, “It's probably the treatment” and that's as far as I go. But for these things, they feel fairly specific. I guess, this is my long-winded way of asking, “Do you typically have these patients see rheumatology when they manifest these symptoms or what does that help look like for you?”

Christian: For sure. Paul, first of all, I would say that if we had a patient together that was going through this therapy, I hope you would call me and say, “Hey, Christian, what hell hath you wrought?” Right?

Paul: Desultorily, yeah.

[laughter]

Christian: Yes. That I think the communication and we were chatting just before we started, one of the reasons I love being an oncologist is for a season of time, I do want them to call me first. However, I know that if they can't get us and they trust their primary doctor, it could come to either of us. I do think that the prescribing physician, the oncologist is responsible for tight communication with the internist or the family physician, and may serve as a reasonable quarterback to consoled out. But I would absolutely ask for help for endo.

I know how to start a lot of stuff, but I don't know exactly how to stop it or how to adjust it. My eyes get blurry when I look at all those anti-thyroid tests. So, I'm not going to order them. I do think you're going to have to take first action. We can all diagnose hypothyroidism and begin therapy. However, I think co-management with an endocrinologist for this is not a sign of weakness. It's a sign of strength. And as far as rheumatology, it's really hard to get anybody into rheumatology in general, but I would make a phone call for this patient.

Nora: We've talked a little bit about the different endocrine conditions, but not in a ton of detail yet. So, we've gone through the common rheumatologic conditions, but what are the common endocrine conditions?

Christian: Right. The most common is hypothyroidism and hyperthyroidism, of course, can happen as well, but it tends to be subclinical and not really presenting with storm. It can happen as well, but hypothyroidism is the main one you're looking for. Diabetes can happen. It's uncommon and this is interesting. The A1c doesn't really help us because the onset of diabetes tends to be sudden. It can even present when it does happen with DKA about 70% of the time. I don't really think there's a way to screen for that. My checking glucose every six weeks isn't going to help. I think being aware and just

talking about the poly symptoms and just really, we want to know when something changes, that's the way I would deal with that.

The hypoadrenalism, that is actually more common than diabetes. Dr. Eck shares a case that I thought was great in a patient that was on a checkpoint inhibitor in combination with chemotherapy, so that would be common in breast cancer and in lung cancer. We give out dexamethasone like a PEZ dispenser to prevent nausea. She has a great case that you're checking your lab and “Oh, no, the morning cortisol is really low” and it turned out it was being suppressed by the dex. So, that's another caveat that I would say that my partners, we need to recognize is not only the 8 AM lab is new, the specificity of that, but making sure you do it before you start the antiemetic prep with dexamethasone would help prevent some false positives there.

Molly: Are most of these conditions permanent or they are temporary?

Christian: It's a good question. We'll just go in reverse order. The endocrine disorders are the ones that don't tend to get better. Would I trade hypothyroidism for 20% chance of being cured from metastatic melanoma? You bet. Take Synthroid all day. But the endocrine disorders are the ones that do not tend to get better. Dermatitis gets better, the colitis, which can mimic inflammatory bowel disease gets better, doesn't persist like inflammatory disease. Most of them get better with the exception of endocrine.

Of course, vitiligo is going to cause what it causes. But most of the time, if you stop the checkpoint inhibitor, and treat it, we can segue now like, what are the most common treatments for it, first thing is you stop and the second thing is just as you would think of just the utility tool for autoimmune disease, steroids. The doses could range anywhere from modest 20 milligrams a day to enormous a gram of Solu-Medrol for people in neurologic crisis or cardiac myositis crisis.

Paul: I guess, that actually touches on something I wanted to ask about in terms of-- I recognize these are new agents and these complications are relatively uncommon, but does background risk affect the potential for risk of side effects? Specifically, for diabetes, if you have family history or so you're prediabetic before, and then you start these medications, does that increase your risk for diabetes, or if you have a history of autoimmune disease in your family, or even personal history, does that increase your risk for these complications?

Christian: It is a great question that was not answered by the clinical trials since people at least with personal history of autoimmune disease were excluded.

Molly: True.

Christian: What's happening now really with Phase 4 is you're getting people where you can use it, and observe, and look back. Personal history of diabetes or family history of diabetes to the best of my knowledge was not an exclusion and does not affect the onset of diabetes, which is still thankfully pretty rare as a side effect. If somebody has a background or family history of autoimmunity, can you do it or not? A lot of it, I think, is a risk or benefit. Like, how bad is the autoimmune disease are you talking about? I'm hypothyroid or I've got wicked RA. Which one is it and then of what benefit is the anti-cancer

therapy? Are we talking adjuvant setting where it's not required or this really is the best option for symptomatic metastatic disease. So, I'm hoping that if we had this talk again 10 years from now, we'd know more,

Molly: Are there any conditions that would be absolute contraindications to using these agents? It sounds to me like it's really a risk-benefit analysis even with autoimmune disease, but I'm curious,

Christian: As far as healthy people go, people can and do give checkpoint inhibitors to healthy people in their 90s. The challenge that I have that's not very well addressed yet is that I don't think we've changed the role about functional status. If there's a healthy elder that's very different from a middle-aged person with a performance status of three and four. I feel that performance status four which is essentially bed bound, because of your disease and that's where we'll often meet people in the hospital, performance status three, performance status four. I don't think that immunotherapy is the magic key out of that. I think, unfortunately, we push it and families and patients want us to push it, because of course, somebody wants something that can turn that around. But being bed bound from your cancer, I would consider as an absolute contraindication to immunotherapy.

Paul: Can I attempt, I'm going to try and pull Watto, and recap a little bit, and you guys will let me know how I do.

Christian: [laughs]

Paul: I don't have the same competence that that guy has. In terms of these immune-related adverse events, so, things that could potentially happen. I'm in my mind divided in between rheumatologic and endocrinopathies though, obviously, there's probably a bit of overlap there. In terms of the rheumatologic, these tend to be seronegative regardless of what we're talking about. But otherwise, for all the role to things like sicca, inflammatory arthritis, and then the spectrum of myositis complications on the rheumatologic side of things, and it sounds you treat all those things the same way that you would treat them where they’re seropositive where obviously we get help from the rheumatologist is the big thing and we'd be talking with the oncologist the entire time. But also, steroids for everything, because they make everything better.

Then from the endocrinopathies side of things, it sounds the more common one to be concerned about specifically is thyroid dysfunction, specifically, hypothyroidism, adrenal insufficiency, and then less commonly diabetes, though that is something that we should be mindful of. Again, it sounds like you manage those in the same way that you would manage them even in the absence of the checkpoint numbers, but you would probably stop the agents if they were significant enough and then treat appropriately. It sounds the endocrine complications are less likely to go away after they manifest themselves. Is that all accurately correct?

Christian: It is.

Paul: Okay.

Christian: It is. The thing I'll add is that if we go outside of the categories of endocrine and rheumatologic, if you think about an organ, it can be inflamed. Pneumonitis doesn't fit in either of those categories, hepatitis doesn't really fit in either of those categories. But I just remember the old programming string you would do StarDot something.

Paul: Yes.

Christian: StarDot inflamed, StarDot-itis.

[laughter]

Christian: So, this is a StarDot-itis. You can get an 'itis' of anything.

Molly: And I'm assuming we treat those all -

Molly: and **Christian:** -with steroids.

[laughter]

Molly: Except for diabetes, which sounds like did not.

Christian: We do not treat diabetes with steroids, doctor.

Molly: Great.

Christian: Yes, I agree.

Molly: Perfect.

Paul: I see it. We don't need endocrinologist.

Nora: You are ready for fellowship.

Molly: Ready.

[laughter]

Paul: All right. I guess, the other question I would have is, if any of these potential side effects manifest themselves and the patient is forced to stop their medication, I'm sure question they might have is, can they restart it, or they start different agents, or how do you manage things moving forward?

Christian: It's a good question and people do ask. If you switch classes of medication, so, go from a CTLA-4 inhibitor to a PD-L1 or a PD inhibitor, there's only a 5% chance of having a recurrence of autoimmune symptoms. It's pretty modest. If you stay in class, it's a 50-50 chance. Most of the time, we

don't restart. Most of the time, you don't have either class as options for indication. There're many more indications for PD-1.

The interesting thing is that it turns out in the clinical trials, the patients who had immune complications did as well as those who didn't and they didn't restart. It may be that there was enough of an immune response, enough of an anti-tumor response that they got the benefit. I would say restarting angels fear to tread, it doesn't happen very often. You would be influenced by how severe the side effect was and how severe the cancer is. If patients get the side effect and stop, it looks like they accrue the same benefit as those on the clinical trials who are able to continue.

Nora: And so, along those lines, do you ever have to answer the question of whether disease is going to be better treated, the cancer is going to be better treated or in the patients that are having those side effects more?

Paul: It must be working, because I feel terrible.

Nora: Right. Exactly.

Christian: That's right, that's right. People are very suspicious of a low toxicity therapy. That's not the way oncology is supposed to work and people do ask that. The interesting thing is you do not and I think a great thing is, you do not need to have an immune-related side effect to have the benefit of the drug. That's great news. It's different from lung cancer when the EGFR inhibitors about 20% of lung cancer has a targetable mutation that you can treat with a TKI. These are the only people you'll ever meet in your life that are happy to have acne, because the acneiform rash of an EGFR inhibitor is absolutely correlated with better outcomes and better survival. So, it's not the same here.

The one exception, which actually makes sense, it makes a lot of sense is that in treating melanoma if a patient develops vitiligo, an autoimmune attack on the melanocytes, they do better. So, these would be the only people on Earth that would be content to say, "I will take the vitiligo." Thank you.

Molly: When patients are doing well and you've seen a clinical response or radiographic response, how long do they typically continue on treatment?

Christian: If it's being used for metastatic disease, it's essentially you continue on either to intolerance or disease progression. So, you may have patients who have been on checkpoint inhibitors for years.

Molly: And do you have just a general sense of response rates?

Christian: Well--

Molly: That's okay.

Christian: I think I know it's fair.

[laughter]

Molly: Because it's variable, I'm sure, but.

Christian: It's variable and I think we also have to just be realistic about oncologists are not the hardest people in the world to excite.

Paul: [chuckles]

Molly: Yeah. But these are exciting.

Christian: With melanoma, which has the most mature data with a real metastatic melanoma about 20% of people will be cured. That is compared to maybe 1% to folks who are known to have spontaneous remissions likely immune related. So, it's not great. It still means that eight out of 10 people have died in 10 years, but a one out of five chance is very different than a one out of 100 chance.

Molly: Absolutely.

Nora: I feel like we maybe should have asked this a little while ago, but are there any risk factors for developing these side effects that you screen for or ask patients about? It sounds not like a diabetes family history, not necessarily.

Molly: Did we talk about this?

Nora: Did we talk about all of this?

Christian: Well, it's an interesting question. I would say that active autoimmune disease angels fear to tread and I would get help and look deeper.

Nora: Okay.

Christian: But people have also been saying, “Well, why does some people react this way and others?” There's one that's just a handwaving, it's your genetics, [crosstalk] what genetics.

Nora: Yeah.

Christian: But the one that's cool is people are starting to look at the gut microbiome. I thought that's pretty amazing because the gut microbiome, there's a lot going on there. Is it immune related? Probably. How? I have no idea. But I think it's certainly not primetime, but that's fascinating to me.

Nora: Yeah, no, in that NEJM piece, they referred to having-- I'm going to totally butcher the name of this. Bacteroidetes phylum and having higher rates of that was associated with reduced rates of ipi-related colitis. So, very interesting. It sounds like not ready for primetime. [crosstalk]

Molly: So, no fecal transplant.

Nora: Yeah, no. Exactly. Just everything.

Christian: Off target comment. There's a book called *We Contain Multitudes*-

Nora: Oh, yeah.

Christian: -about the microbiome, which is fascinating. I don't think they're going to do stool transplants, but there's a lot there.

Nora: It's cool.

Paul: Yeah, it's so interesting and the microbiome everywhere that we're now starting to recognize that exists, but yeah, that's a different episode, probably.

Nora: Sorry. It took us on a wild tangent there.

Christian: Tangent.

Paul: Bacteroidetes.

Nora: Obviously, we're very excited about checkpoint inhibitors already. In terms of immunotherapy places we're going, what are you excited about coming down the pipeline right now?

Christian: There's something I'm excited about that is now and there's something I'm excited about which I think is coming. My practice was autologous transplant. In essence, you just do apheresis, you take out GCSF mobilize stem cells, and then you just put them in the freezer, give a huge old dose of chemotherapy, and give them back. All you're really doing is pushing the chemotherapy response dose past what the marrow can tolerate and then you're just rescuing the marrow.

The new kid on the block is something called CAR T-cells and CAR stands for chimeric antigen receptor, where you essentially do the same process. You take out the stem cells, separate the T cells, and then a chimera, I don't know like a liger or something like that.

[laughter]

Christian: You put a receptor, an antibody receptor on a T cell that does not occur in nature. It has cured young adults with ALL or with aggressive B cell lymphomas. It is being used in most tertiary and almost all quaternary cancer centers now. It can be sepsis in a jar, the cytokine release storm is severe, it can actually be treated with an IL-6 antagonist called tocilizumab, which was used for rheumatoid arthritis. There's some cool crossover. You have to be excited about CAR T if you're an oncologist or they'll take away your card.

The one I'm really excited about is what about CRISPR-Cas9 editing for something like sickle cell anemia. It's a single point defect. It was the first described genetic disease. Allogeneic transplant can cure sickle cell anemia, but allogeneic transplant just beats the heck out of people. If you could edit sickle cell anemia and I just heard a podcast with Jennifer Doudna talking about the work they're doing with it, that would be a game changer. So, that's what I hope is coming. That's what I'm looking forward to.

Paul: Excellent.

Nora: Very cool.

Paul: Super exciting. I think this is a good place to draw to a close, now that we're talking about the future. Christian, can I ask you what are the main take home points you would have for our listeners about this checkpoint therapy?

Christian: For sure. The main point is just be aware that you're going to be seeing in more and more patients, the indications, particularly in solid tumors are growing. I think we're used to the cutting edge, the Nibs, and the Mabs happening in heme malignancy first. That's probably true because the biopsy is easy. You just draw blood. The solid tumors now are getting a renaissance and so patients with bladder cancer, with lung cancer, with breast cancer, with colon, you will see these medicines. If you think about the fact that the treatment and the side effects are just two sides of the same coin. If they are immune treatments, then autoimmunity as a side effect makes all the sense in the world and then we can just go down through the characterization that you said, there's endocrine and rheumatologic, and then StarDot-itis for everything else.

Paul: Great, excellent. Anything that you'd like to plug while we have you here?

Christian: I would like to plug The Stihl MS-462 Chainsaw that I referred-

[laughter]

Christian: -as Rachel the IV.

[music]

Paul: This has been another episode of the Curbsiders bringing you a little knowledge food for your brain hole.

Molly: Yummy.

Nora: [laughs]

Paul: Wrong. Get your show notes at *thecurbsiders.com* and while you're there, sign up for our mailing list to get our weekly show notes in your inbox, plus twice each month you'll get our new Curbsiders Digest recapping the latest practice changing articles, guidelines, and news in Internal Medicine. We are committed to providing you with high value practice changing knowledge and to do that we need your feedback. So, please subscribe, rate, and review the show on Apple Podcast or contact us at *thecurbsiders@gmail.com.*

Molly: Special thanks to our writer, producer and cohost for this episode, Nora Taranto and to her whole team. Beth Garbitelli is our executive producer with production and editing support from the team at Pod Paste. Elizabeth Proto runs our social media, Tima Karginov maintains our website, Stewart Brigham can post our theme music, and Chris "The Chiu" Chiu has been our audio engineer today. Until next time, I've been Dr. Molly Heublein.

Nora: I've been Dr. Nora Taranto.

Paul: And as always, I remain Dr. Paul Nelson Williams. Thank you and goodbye.

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