Diagnosis and Management of Immune-Checkpoint Inhibitor Skin Toxicity

Steven Chen, MD, MPH, FAAD, interviewed by Carlos Garcia, MD

CARLOS GARCIA, MD: Welcome to another episode of *Dialogues in Dermatology*. I am your host, Dr. Carlos Garcia, from Oklahoma City. Today, I have the pleasure of speaking with Dr. Steven Chen, from Harvard University, about a scientific session that he participated in during AAD 2024. The title of the session was "Advanced Therapeutics For Complex Dermatologic Diseases." Steven, thank you for taking the time to talk to us during this interview.

STEVEN CHEN, MD, MPH, FAAD: Carlos, thank you so much for having me.

CARLOS GARCIA, MD: Why don't we start by asking you, what was this session about in general, just a brief overview or summary of this session?

STEVEN CHEN, MD, MPH, FAAD: I think the simple way that I put it during the session, just to make it simple for everyone, is what do you do after topical steroids? We're so good with topical steroids, topical azoles, all the topical medications, but when we have to reach for systemic medications for a variety of complex disease, what should we be thinking about? So I was able to invite six of my closest friends, mentors, mentees, to come chat about a variety of complex skin disease that we might take care of in the course of our career.

CARLOS GARCIA, MD: Which diseases did you guys talk about?

STEVEN CHEN, MD, MPH, FAAD: We covered cutaneous lymphomas, graft-versus-host disease, hidradenitis suppurativa, the autoimmune blistering diseases, neutrophilic dermatoses, connective tissue diseases, and I myself spoke about dermatologic immune-related adverse events from checkpoint inhibitors. So we covered quite a broad range of disease topics.

CARLOS GARCIA, MD: A very impressive list of complex derm diseases. If I could ask you to give us two or three take home messages from that session for the general derm, we're not in

Harvard, we're not academics all of us, so we're in a day-to-day derm clinic, what should we remember about this session?

STEVEN CHEN, MD, MPH, FAAD: First of all, I could say everyone could be at Harvard. All of us could be practicing the same type of dermatology that we're practicing anywhere. I think the most important thing is to have a network for dermatologists that you can ask questions of. I think that really shone through yesterday in the session. A lot of conversation about who I ask for help, when I ask for help. Sometimes it's not even a dermatologist. You reach out for help from an oncologist or a rheumatologist. I think the other big takeaways from yesterday's session really, one is that we as the dermatologist have a lot to offer.—

--We really can go pretty far in terms of systemic therapy, in terms of monitoring for adverse effects, in terms of combining therapies with other ones that other specialists might not be very familiar with. So we really have an opportunity as a specialty to push ourselves forward in medical dermatology. That was a big, big message that was sent in yesterday's session. And then the last thing just to touch on specific therapeutics, because I think we're always thinking about classes of medications that are new and interesting.—

--I don't think it's a surprise to anyone to say that JAK inhibitors are kind of the one class of medications that are being tested across the board in many of these disease states. So it will be really exciting to see where that goes. Of course, new biologics that are being developed in a variety of pathways to help. And there's a lot of borrowing from one disease state to the other. For example, using biologics from psoriasis in the treatment of hidradenitis.—

--Or using biologics across the board for cutaneous lupus and for a lot of our inflammatory states. So that was kind of the overall message that was sent, at least that was my takeaway as the course director yesterday.

CARLOS GARCIA, MD: What a wonderful time to be in general derm, when we now can take care of patients, do good, learn basic science, be upfront on the scientific progress of our specialty. Among all these things, one topic that is of personal interest to me would be the immune checkpoint inhibitors. Because I think they have revolutionized the treatment of cancer. I know overall these agents are going to have a very favorable profile, but their use has been associated with specific toxicities that may potentially affect treatment.—

--Let me start by asking you to define what are these so-called immune-related adverse events?

STEVEN CHEN, MD, MPH, FAAD: As we're very familiar with now, checkpoint inhibitors are using the immune system to fight cancer, but because we're doing that it's also potentially going to fight self and fight the patient's other cells, other tissues. So an immune-related adverse event is any adverse event that we think is immune-mediated from the checkpoint inhibitor. And those of the skin we just call dermatologic immune-related adverse events or cutaneous immune-related adverse events.—

--We actually talked about in the session yesterday, there are some new diagnostic criteria that we're really excited about that were developed with 34 experts across the world by Delphi consensus process that we were really excited to bring forward and was just accepted to the *Journal of Immunotherapy for Cancer*. That whole process has allowed us to redefine how we actually diagnose these diseases. Because I think it's been very haphazard, to be honest. Most of them were just called maculopapular rash until now, when we actually have diagnostic criteria for more specific morphologies.—

--So I think now that that's been accepted, we'll hopefully see some more specificity going forward and it will help us out with caring for patients and for clinical trials, everything related to this field in the future.

CARLOS GARCIA, MD: Of course, we will deal with the skin manifestations of this. But there are other organs involved. So the dermatologist I think has to be aware that the patient that is coming with pruritus and a rash may also be sick from other organs. What are the most common organs affected in this type of reactions?

STEVEN CHEN, MD, MPH, FAAD: The reason why we as dermatologists have to be familiar with this is because the skin toxicity from checkpoint inhibitors is not only the most common, but they're the earliest. So patients often get referred from the oncologist to the dermatologist first. And then we might be one of the first subspecialists to actually identify a potential other organ that's involved. So the ones that we think about in particular, gastrointestinal toxicity is quite common. Rheumatologic toxicity, where you see arthritis and myositis is another one that we often see, too. –

--There are endocrine toxicities. Basically, you name it, you got it, like it's possible. The ones that are less common but devastating would be the cardiac toxicities. So that one we don't see all the time. However, that's the one that lands you in the hospital and that's the one that carries a high mortality rate with it. And then, of course, you can hit hepatitis, pneumonitis, but if it's in the body, it can be attacked by the immune system and that's the problem with this class of drugs. It's an amazing class of cancer therapy but it's a double-edged sword. It comes with this potential for toxicity that sometimes can be quite morbid or can even be fatal.

CARLOS GARCIA, MD: How common are these reactions? For example, I work closely with a group of oncologists, and I really do not see many of these reactions. I might be missing them, of course, but I doubt it because of the clinical scenario, the type of referrals. So are the oncologists taking care of this? How is it that I don't see them frequently?

STEVEN CHEN, MD, MPH, FAAD: They are very common. There was actually a nice paper that showed that if you combine ipilimumab and nivolumab, which is a CTLA-4 inhibitor and a

PD-1 inhibitor and that's one of the most common combinations we use for metastatic melanoma now, you can actually get a reaction in up to 72 percent of patients, which is very common. So there are other papers that quote even higher prevalences for dermatologic immune-related adverse events. It's no surprise to me that you probably aren't seeing a ton of them and that's exactly for the reason that you mentioned, which is oncologists are taking care of these toxicities.—

--While that's great and we want them to feel comfortable doing that, the main issue with oncologists taking care of it is that they follow their own set of guidelines, which really is not specific to the actual skin toxicity that they're seeing. So what I mean by that is everyone is getting topical steroids, everyone is getting prednisone, everyone is getting antihistamines, but then not much else after that. So I think we have a lot to offer. For example, if someone comes in with a checkpoint-induced lichen planus-like rash, we know as dermatologists, you know what, maybe we can add hydroxychloroquine or maybe we can add acitretin.—

--And these are medications that oncologists would not be familiar with. So a large part of the work that we do in this field is to try to encourage oncologists to refer their patients to dermatology, because I think they don't really understand how much more can be done than just systemic topical steroids and holding the checkpoint inhibitor.

CARLOS GARCIA, MD: You were mentioning lichenoid reactions, I think eczematous reactions. In your experience, can you name the most frequent cutaneous reactions to these agents, besides dose too?

STEVEN CHEN, MD, MPH, FAAD: Actually, that's how I framed my talk yesterday, which is the top ten most common reactions, based on insurance claims data. Now that I'm on the spot, I probably won't remember all ten but we'll try to hit some of the more common ones. Anecdotally, just being in clinic, we talked about the lichenoid. You can have checkpoint-

induced pruritus, with or without a rash. As you mentioned, you can have an eczematous reaction. You can have a psoriasiform reaction. What we now are renaming ICI exanthem, and that's supposed to encompass the morbilliform eruption or perhaps the dreaded dermal hypersensitivity reaction that we all see on biopsy.—

--In addition to that, there's Grover's. There's an erosive mucocutaneous eruption, think of it as almost like Stevens-Johnson or bullous lichenoid eruptions, that's obviously more severe. And then the other couple that are big would be vitiligo and then bullous pemphigoid is also commonly seen, too.

CARLOS GARCIA, MD: I didn't know there was such a wide variety of reactions.

STEVEN CHEN, MD, MPH, FAAD: Actually, just to mention that this is a common quote that I think is attributed to many people now. But an easy way to think about it is checkpoint inhibitors cause dermatology. So it's anything under the sun has been reported from checkpoint inhibitors but those top ten are the ones we should be familiar with.

CARLOS GARCIA, MD: That's a very nice way to think about that. So in general, what is the prognosis of these rashes? Because you mentioned that some can be life-threatening. If you could tell us in general what to expect from these patients? And then which ones are the ones that we have to really pay attention to because they can become grave?

STEVEN CHEN, MD, MPH, FAAD: If you ever see a checkpoint inhibitor toxicity patient, one of the first things to do is to grade their severity. So we adapt from the CTCAE grading, so if the rash is less than 10 percent, it's grade 1; 10 to 30 percent is grade 2; greater than 30 percent is grade 3. And then once the patient is affected enough that it's affecting their activities of daily living and they might need to be hospitalized, that's a grade 4 rash. Obviously, the rashes that

are grade 4 are the most concerning but you're worried about your grade 3 rashes that could move into a grade 4.—

--So really looking at BSA is one of the first steps to do. The next thing to think about is your morphology. So if you're seeing blisters on the skin, if you're seeing a positive Nikolsky, those are great reasons to get the patient into the hospital. We're very fortunate in dermatology that these toxicities in general are as a whole more mild than toxicities of other organ systems. The severe ones do exist and I unfortunately have seen patients die from the immune-related adverse events of the skin, but that is definitely few and far between compared to most patients who can be managed in the outpatient setting.—

--One study that we did at our hospital actually showed that we're good at treating these, but very rarely can we completely clear the patient of their rash. So what we really need to do is to think about our goal as the dermatologist. My goal when I treat these patients is not to clear their rash but it's to decrease the burden of skin disease and symptoms to the point that it's tolerable. So putting that in grades, if I have a patient come to see me and they have a grade 2 or 3 rash, I tell them my goal is to get them to a grade 1, so that they can be back on therapy and be comfortable at home, get some sleep, and not be focusing on their skin all the time.

CARLOS GARCIA, MD: Do you remember any particular patient that died? And what was the background, what was your intervention, and when did you decide to stop or continue treatment? What happened with that particular patient?

STEVEN CHEN, MD, MPH, FAAD: When patients pass away from this group of diseases, which is obviously not what anyone wants, it's a very sad situation overall, they're in the hospital. When they're in the hospital, usually what happens is that we realize often it's because it's complicated by other organ systems at that point. Skin itself, if there's no complications, we are pretty good at being able to stop what's going on. Even if someone comes in with what

looks like a Stevens-Johnson from a checkpoint inhibitor, because we know that this is immune-mediated and inflammatory in nature because of the mechanism, often if you can give enough prednisone or being able to give IVIG in certain cases, only in certain cases it's a little complicated, but we can usually turn that around.—

--It's when patients start to obviously become septic from their eruption or maybe they have another IRAE of another organ system, that's when it gets really, really tough. One thing that I'm very fortunate to have at our hospital is we actually have a severe immunotherapy complications service, where we have specialists from every organ system that come down and take care of these patients together. Obviously, these patients still are very, very sick and unfortunately you can't save everyone. But that is a place where collaboration is so important because often, what the hepatologist or cardiologist is thinking about might be in line with what you're thinking about and being able to sit down and come together and come up with a plan that hopefully helps the patient is really rewarding.

CARLOS GARCIA, MD: Are there any other teaching institutions that have that kind of approach, multispecialty in a particular place where everybody works together?

STEVEN CHEN, MD, MPH, FAAD: Yes, absolutely. Many large academic centers have already started these types of multidisciplinary teams. I think we're fortunate that at Mass General, we had one of the earliest ones, but that's not to say that we were the first. I think it's just that people are starting to realize that this team approach is so critical specifically, especially for these patients. I think the work is now being replicated even internationally at other cancer centers across the globe.

CARLOS GARCIA, MD: Obviously, this type of reactions are a clinical diagnosis, right? Epidemiological and cutaneous findings, etc. But are there any instances when you can

recommend certain bloodwork tests or skin biopsy? And how does that help you once you know that clinically this might be the issue?

STEVEN CHEN, MD, MPH, FAAD: I think first of all, that Delphi consensus diagnostic paper that we recently had accepted, what I want to highlight is that all of it is actually based on morphology. So the dermatologist really sits in a really unique position that we can make those diagnoses often without a skin biopsy. In other words, you see a psoriasiform eruption, you can pretty comfortably say this is a checkpoint-induced psoriasiform dermatitis.—

--The way that the Delphi diagnostic criteria laid out, it's nice because if an oncologist sees a rash and they are not sure what the morphology looks like, we take them down a path where they can actually do a recommended workup. And then that workup might be able to get them to one of the diagnostic criteria. Now, to get to your point about what we as dermatologists should be doing in terms of bloodwork, in terms of biopsies, one study we did showed that our ability to predict the histologic findings, our own clinical pathologic correlation is not quite as good in this group of diseases compared to general dermatology.—

--So my threshold to biopsy these patients is lower compared to the rest of my practice. The other thing I would highlight here is that because it's so morphology-specific, you really want to treat based on morphology. So I don't want to give a drug that I think would help an eczematous patient when they actually have a lichen planus-like rash. Because we've gotten into trouble sometimes where sometimes that might even flare their lichen planus-like rash and we try to use a medication that's more appropriate for a spongiotic dermatitis. So that's why biopsies are important.—

--In terms of bloodwork, the one thing I emphasize for our oncologists to think about is we've also shown that checkpoint-induced bullous pemphigoid, which is a very common reaction that requires stopping of the checkpoint inhibitor, often has a rash-free pruritis beforehand. So

ELISA's from the blood for bullous pemphigoid antibodies, that's something that we tend to recommend for patients who just come in with pruritis without rash.—

--In addition to that, we're often doing our normal labs, our CBC with differential, our comprehensive metabolic panel, but then specifically looking at IgE levels because that opens up for the treatment with certain biologics. And then for admitted patients to the hospital, we'll also get an IL-6 level because one of the ways we treat these patients is with tocilizumab, which is an anti-IL-6. So it really is largely focused on gearing up for downstream treatment. The exception to that would be the bullous pemphigoid ELISA's, which we send a lot in our itchy patients.

CARLOS GARCIA, MD: Would a skin biopsy help in that case, when we have pruritus?

STEVEN CHEN, MD, MPH, FAAD: Skin biopsy in the case of pruritis is certainly helpful, if there is any suspicion of an underlying subclinical eruption. The issue is that rash-free pruritis is so common in this group of patients that I don't think it's feasible for us to say that we're going to biopsy every single patient. So what I do is I biopsy anyone who comes in with pruritis where I can maybe see there's a little bit of erythema, even super-faint erythema I'll go there, because maybe I'll pick up the morphologic findings on histology that guide my treatment afterwards.

CARLOS GARCIA, MD: Unfortunately, we ran out of time, Steven, but this has been awesome. Thank you again for this interesting and informative interview. I learned a lot and I'm sure our audience will, too.

STEVEN CHEN, MD, MPH, FAAD: Thank you so much for having me. It's always a pleasure to be on *Dialogues* on this side of the microphone, as well. But thanks so much for chatting this morning with me.

CARLOS GARCIA, MD: Well, friends, I am Dr. Carlos Garcia, from Oklahoma City. This was another episode of *Dialogues in Dermatology*. On this occasion, I had the privilege of interviewing Dr. Steven Chen on the topic of the therapeutics for complex dermatologic diseases, and in particular also about the reactions that we can see when we use immune checkpoint inhibitors. I hope you enjoyed it as much as I did, and we'll see you next time.

Commentary

Eryn Patin, BS and Sarah D. Ferree, MD with Benjamin Stoff, MD, FAAD (ed.)

The immune system is designed to readily distinguish self from non-self. Cancer cells exploit immune system checkpoint proteins, to evade detection and destruction. Immune checkpoint inhibitors have revolutionized cancer therapeutics by inhibiting these checkpoint proteins, enhancing the immune system's ability to identify and attack cancer cells.[1] While this new class is highly effective in treating cancer, it has been noted to cause various immune-related adverse events to multiple organ systems including the skin. In this episode of Dialogues in Dermatology, Dr. Carlos Garcia interviews Dr. Stephen Chen of Harvard University about the various dermatologic adverse events related to checkpoint inhibitors and how dermatologists should manage them.

5 Key Takeaways from Today's Episode include:

1. Checkpoint-inhibitors can induce an immune-related inflammatory reaction that can be toxic to any organ in the often the skin.
2. Checkpoint inhibitors can cause numerous adverse dermatological reactions, including immune checkpoint inhibitor exanthems, lichenoid eruptions, checkpoint-induced pruritus, eczematous reactions, psoriasiform reactions, Grover's disease, erosive mucocutaneous eruptions, vitiligo, and bullous pemphigoid.
3. While these reactions are common, they are often initially managed by oncologists with non-specific medications such as topical and system steroids and antihistamines. By encouraging oncologists to refer patients to dermatologists at the first sign of drug-induced skin toxicity, more targeted therapies can be initiated early in the disease course.
4. When suspicious of a checkpoint inhibitor-induced cutaneous adverse event, dermatologists should:

   1) use the Common Terminology Criteria for Adverse Events (CTCAE) grading system to assess severity. This is determined based on the Total Body Surface Area (TBSA) and impact on activities of daily living.

   2) asses the morphology of the lesions[2]

   Concerning physical exam findings, such as greater than 30% total body surface area involvement or a positive Nikolsky sign, may be indications for hospitalization and more aggressive management.
5. Although immune-related adverse events can often be diagnosed clinically, histologic findings in many cases may be less reliable. Dermatologists should have a lower threshold for further workup, including bloodwork and skin biopsies, in these patients to correctly tailor their treatment plan.[3]

Thanks for listening to Dialogues in Dermatology!

References

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