

Nonsurgical Treatment of Basal Cell Carcinoma

Scott Dinehart, MD, interviewed by Steven Chen, MD, MPH, FAAD

STEVEN CHEN, MD, MPH, FAAD: Welcome, everyone, to another episode of *Dialogues in Dermatology*. Today, we are going to be talking about nonsurgical treatments of basal cell carcinoma. My name is Steven Chen and I am so excited to be speaking with Dr. Scott Dinehart today about the topic. Scott, welcome to *Dialogues*.

SCOTT DINEHART, MD: Thanks for having me.

STEVEN CHEN, MD, MPH, FAAD: If it's okay, we're going to jump right in because there's a lot that we can talk about on this topic. So just to start off thinking about basal cell carcinoma, I think we all think of it as primarily a surgical disease. We know when to excise it, we know when to refer to Mohs, we know how to ED&C it, depending on the subtype of basal cell that we have. But maybe just to start, could you fill me and our listeners in on when we might be thinking about nonsurgical treatments for basal cell? What are the indications? What are the times that we're reaching for this? Are there certain syndromes that might lead us to be thinking about some of the more medical management side of things for this diagnosis?

SCOTT DINEHART, MD: I think you're correct, it's mostly a surgical disease. But there are a small number of patients who, for one reason or another, it's not a surgical disease. And I think people tend to think of these as kind of the pancake, the pizza-type lesions, the huge lesions, and we will talk about some of those. But also think that hopefully people will expand the use of some of these treatments, like Hedgehog inhibitors and cemiplimab to smaller, more troublesome lesions.—

--Sometimes it's not just the tumor characteristics, it's the patient characteristics. Patients are demented, they're in nursing homes. They are ill or have other conditions that keep them from having surgery. They live far away from a radiation facility, because surgery and radiation are

primarily our historical means for dealing with basal cell skin cancer. So then you have to consider other things, like Hedgehog inhibitors. We got a new indication for cemiplimab immunotherapy, we want to talk about that. And then certainly, we do some other things that most people are familiar with: imiquimod for smaller lesions. Imiquimod is also a Hedgehog inhibitor. It's a toll receptor agonist but it is a Hedgehog inhibitor.

STEVEN CHEN, MD, MPH, FAAD: I think that's really helpful for us to remember, that there are multiple reasons to think about why we should choose a nonsurgical intervention for basal cell, including patient characteristics. Before we get into kind of the newer drugs on the market, like the Hedgehog inhibitors and the checkpoint inhibitors, maybe we could talk a little bit about the topical treatments that we could use. One thing I always think about is radiation. How do you think about applying those kind of more locally targeted therapies for basal cell?

SCOTT DINEHART, MD: I'm a big fan of imiquimod. Just a disclosure, I am the second author on the paper that got it through the FDA, so I know a lot about imiquimod. I did the early trials. I love using it for superficial basal cell carcinoma. Unfortunately, we just don't have anything for invasive basal cell carcinoma now that's topical. I do use radiation. Arkansas is where I'm from. We're a very rural state, so sometimes that causes limitations. Because patients have to go for multiple treatments, many days in a row, and sometimes they just can't do that.—

--But certainly radiation is an option, surgery is an option. Also, all these things we talk about, combinations, or we talk about neoadjuvant therapy, where we maybe start with something like a Hedgehog inhibitor, then we go to surgery, or then we go to radiation, or even concurrently we're using both. I'm a big fan of even triple therapy. I've used Hedgehog inhibitor, imiquimod, and itraconazole as a Hedgehog inhibitor off-label. I'll mention that we are going to talk about off-label things here. I've used triple therapy in patients before. So it's a place where there's a lot of innovation and hopefully that's stimulating to our listeners.

STEVEN CHEN, MD, MPH, FAAD: Absolutely. Actually, when you say those kind of treatment regimens that you're using, the first thing that comes to mind is who, if anyone, are you partnering with? Is this all kind of driven by you, the dermatologist? Or are you reaching out to a colleague in oncology to help you out? Obviously, one would also think about radiation oncology sometimes, if we're reaching for radiation. I'm curious, who is your team, if you have one? What's your practice pattern like?

SCOTT DINEHART, MD: That's a great question. I always tell patients it's not just about me. I have a great team. I have great histo techs, I have great nurses, my reception, everyone. It's a team effort, as you know. One of the things I think listeners should take home from this, one of the most important things is that you can do this. You should do it. You can keep these patients in your practice and use Hedgehog inhibitors. It's something that you can do. You don't have to send them to someone else. It's very gratifying. And usually, it's that person in the practice that has a little bit of a medical bent.—

--My friends are all Mohs surgeons and they like to do surgery, they don't like to deal with medical things. But that person that has a medical bent or even a well-supervised midlevel provider, I know they don't like to be called that, but a nurse practitioner or a PA that's well supervised, they could do this in your practice. But it's not something you have to refer out. I want to emphasize that you can do it and you should. They're underutilized and they work better than advertised, the Hedgehog pathway inhibitors do.—

--Now, for cemiplimab, which we'll talk about later, the immunotherapy, you do have to partner with an oncologist because it's an infusion, it's a PD-1 inhibitor. It has some side effects and it can occasionally land you in the hospital, so you want to partner with an oncologist. But you want to have that relationship where that oncologist knows that you work well with, that when

you send them a patient, they know exactly what to do with them. And I still follow along but again, it's somebody I partner with.—

--I do partner with the radiation oncologist. I tend to send my patients to the oncologist first, because I know that if they need a radiation oncologist, they'll get them involved. I've had some problems where surgeons still want to be surgeons and if I send them to a surgeon that's working with maybe the oncologist or at a big cancer center, I think sometimes they are still in the days where we do surgery that's difficult for patients, whereas maybe I feel like they should have gone for the immunotherapy or the Hedgehog inhibitor or something else. I feel like the oncologists will get those surgeons involved when they need to, if they need to.

STEVEN CHEN, MD, MPH, FAAD: I'm all for keeping things in the dermatology circle, dermatology family, as much as we can. Understanding that there are just some places where we do have to partner with our colleagues because of maybe institutional guidelines about who is allowed to prescribe what. But since you mentioned cemiplimab already, maybe we could start there and talk a little bit about how that recent approval for basal cell carcinoma, when do you think about using cemiplimab? What do you counsel patients on before you send them to oncology perhaps? How do you think about this drug in the treatment of basal cell?

SCOTT DINEHART, MD: First of all, I want to say cemiplimab has been a tremendous advance for our squamous cell patients. I know that you think this also, it has been something, I think maybe the listeners don't know this, squamous cell carcinoma kills more people in this country than melanoma. And I'll say that again because I'm not sure that that resonates with people, that more people die in this country of advanced squamous cell than basal cell. So we have gotten a taste that cemiplimab with our squamous cell patients, it works very quickly, it works very well.—

--Sometimes we combine it with surgery later. But we've just recently gotten this approval for advanced basal cell carcinoma. Now, I'm one of those people, I get a tremendous amount out of my Hedgehogs. And so I have a couple of patients on cemiplimab but one of the things you need to know is that cemiplimab is given by the oncologist. It works very quickly in squamous cell but maybe not as quickly in basal cell. So you have to be a little more patient. I'm in that patient phase with a couple of my patients.—

--The times when I use it are when patients have resistance. And that can be seen, I see that occasionally. I use so many Hedgehogs that I do see resistance sometimes. Sometimes, you can get a lot out of your Hedgehogs but you just can't quite finish a patient off. And I have one patient now that's on cemiplimab for that reason and I'm hoping that I can finish him off with the cemiplimab and get a cure. Also, I sometimes get patients, we'll talk about how I minimize adverse events, but sometimes I get patients who have had Hedgehogs from other providers and they didn't minimize those adverse events and the patient just comes in not wanting to be on the Hedgehog.—

--And so those patients go to cemiplimab. The indication is such that you're supposed to use Hedgehogs before going to cemiplimab but there's a little bit of wiggle room there. If you don't think it's appropriate, you can go directly to cemiplimab. So you have some wiggle room, you can do what you think is best for the patient.

STEVEN CHEN, MD, MPH, FAAD: I think that this is just kind of me waxing poetic a little bit about our specialty, as someone who personally specializes in the toxicity of cemiplimab and its related agents as checkpoint inhibitors, it's interesting to think about how varied our specialty is, where you could sit on one side and focus on the treatment of the tumor, or sit on the other side and focus on the treatment of the toxicity. But as someone who's seen a lot from checkpoint

inhibitors, I naturally feel a little bit more cautious about knowing, since I know all that can go wrong with something like cemiplimab.—

--Whereas vismodegib or other Hedgehog inhibitors that we should talk about next, I'd love to hear your take on the adverse effects profile for Hedgehog inhibitors, just because to me at least, as someone who admittedly doesn't reach for these all the time, to me at least it seems like it's a little bit more self-limited. It's a little bit less of a kind of black box, in terms of knowing what you're going to get from your patient. So maybe we could go to the Hedgehog inhibitors and tell me a little bit more about how you use those, how you do mitigate the adverse effects from using a Hedgehog inhibitor?

SCOTT DINEHART, MD: As you know, I'm a big fan of Hedgehog inhibitors. We do have two that are approved for basal cell carcinoma: vismodegib, sonidegib. And basically my message to people is that efficacy is not a problem. I think that most experts, including myself, believe that over 90 percent of patients will get benefit from these medications. What is a problem, as you mentioned, are the adverse events. Up to 25 percent of patients and probably more will discontinue therapy because of adverse events.—

--My two tips, my two take home tips for listeners are, number one, decrease the frequency of dosing. I like to decrease from every day dosing to 10 to 15 days per month. And I get great results with that. And again, you mentioned you're not going to crush anybody with Hedgehog inhibitors, and particularly low dose inhibitors. So you see the little old lady in the nursing home with the bleeding lesion that's getting infected, you know you're not going to crush her or land her in the hospital with Hedgehog inhibitors.—

--My second tip is to use L-carnitine for the muscle cramps. As you know the big three are muscle cramps, alopecia, taste disturbances. Muscle cramps are perhaps the most onerous and a lot of people discontinue because of this. So if you decrease the frequency of dosing and you

use L-carnitine, which is an amino acid, you can buy it at a health food store or on Amazon. I actually buy this stuff and keep it in my office. And when I start a patient on, I hand them the stuff and tell them where to get it. And I have them start it before I start the Hedgehog inhibitor.—

--And that way, it reduces the muscle cramps. They're on a lower dose anyway. A lot of my basal cell nevus syndrome patients are on 10 a month, they've been on 5 or 6 years, and they tolerate this very well. So those are my two big tips. Again, I think dermatologists are the experts in skin cancer. We should do this for our patients. And trying to send this off to someone like an oncologist, I understand the oncologists are very good and they can handle this, but I think that we are the experts, we should be doing this. This is a dermatology thing.

STEVEN CHEN, MD, MPH, FAAD: I love it. One of the things I always say when I'm trying to sell the field to a potential applicant, a medical student, is dermatology is one of those things where you really own the patient's organ from start to finish, and it's great to hear that. I'm interested, if it's okay, I'd love to chat a little bit about the L-carnitine, because I do use L-carnitine for the muscle cramps and the myalgias that I see when I'm prescribing something like isotretinoin. And so I'm surprised to hear that it also works when you're using a Hedgehog inhibitor. I personally have never been able to figure out exactly what the pathophysiology is or why the mechanism of action of that supplement, for why it works. You, I presume, have looked into it. I'm curious if you have a little bit more insight as to how it works and why it works?

SCOTT DINEHART, MD: First let me tell you that I want to give Dr. Black in Lexington, Kentucky, the recognition for pointing this out to me. I was just having a casual conversation with her and she explained to me that she'd been using L-carnitine in all her patients and she wasn't having muscle cramps. And she had her first patient was a weightlifter who was using this, so she figured out she'd just keep using it. And that was a big epiphany for me. We did a

little study and published it. The Stanford group did a small study and showed there was a dramatic decrease in muscle cramps, so there is some literature out there that supports this.—

--Then when you talk about how it works, there is a mechanism. And what happens is that we don't know, the Hedgehog pathway, I could simplify it for you but as you know, it's extremely complex. It makes you dizzy, just whoever put this thing together, it's just incredible how complex these pathways are. But what we think happens is that the cell, the muscle cells are flooded with calcium. That's why at first we thought, well, let's use some calcium blood pressure medicines, things like that. But what happens is the muscle cell is flooded with calcium.—

--What L-carnitine does is it supercharges your mitochondria. It basically gives those mitochondria the energy to support the pumping out of that calcium. That's how we think it works. So basically, you're supercharging your mitochondria in those muscle cells that are pumping out the calcium and that is keeping you from having the muscle cramps. And that's also why things that work in other types of muscle cramps don't work in these type, doing pickle juice or having people take magnesium or other things, it doesn't work because of the mechanism of action.—

--But I think that's the best science and I think it's supported by good research and that's why we think L-carnitine works. What's amazing to me is that we have this L-carnitine that we buy in a health food store and again, it's one of these alternative medicine type things, where people say, "Well, that doesn't work. This doesn't work." But there's a whole bunch of medical literature that shows that L-carnitine works for other things. A lot of my family docs are giving it to their older patients because it does increase their muscle strength. And as you know, as you get older people tend to fall, they don't have good muscle strength, their tone, that's a problem.—

--A lot of my doctors, when I do send a little letter to them, telling them I'm putting this on the patients, putting them on this medication because I want them to know. And they say, "Oh,

we're familiar with that because we use that in the nursing home." So it's used for other things, also.

STEVEN CHEN, MD, MPH, FAAD: That's great to know. Something that I look forward to discussing more in detail with my residents. If it's okay, I'd love to just kind of pose a patient for you. Like let's say someone comes in, they've got metastatic or locally advanced or the patient characteristics are such that you want to start them on some type of systemic therapy. Would you be able to walk me through what you usually think about? Like what do you start with? I know it sounds like you usually start with a Hedgehog inhibitor, maybe move to cemiplimab to kind of clean things up. But how do you approach that patient that comes in? What's your first move and what comes after that?

SCOTT DINEHART, MD: Let me tell you, I do a lot of these patients, and a lot of patients seek me out or find me, because I'm the one that's willing to do this. But I think that again, one of my messages for dermatologists is you should do this, also. It's very gratifying, your patients will love you for it. And if you're medically inclined, it's really a lot of fun. A lot of times, my nurse already tells me before I walk in the room that this is that kind of patient. And I want to mention that no treatment at all is often in the discussion.—

--So when I see a patient, I come in, if it's the 93-year-old patient in the nursing home and they're not having problems with their lesion and it's not something that we have to treat, many times no treatment at all will be I'll follow the patient. So I think that's always in the discussion. And then you're right, I tend to talk to them a little bit. And a lot of times, it's the patient's decision. We talk about, "I have a pill for this." Sometimes you give them the pamphlet that shows all the side effects and stuff but I say, "But I've got a way to mitigate the side effects. I can cut these down so that they're not a problem for you."—

--And then I always make a deal with them. If it's not getting better in a couple of months, we get off of it. Of course, I told you that almost everybody, Hedgehogs work very quickly, they work fast, and by the time that the patients are having any kind of side effects, which they usually aren't because I'm on lower doses with L-carnitine, they're already getting results and they're generally happy. So that's the discussion.—

--Sometimes I have patients that come in that have been on Hedgehog inhibitors with other people. Again, that's when I'm thinking more let's go to cemiplimab. You talked about you're the expert, I feel a little uncomfortable talking about immunotherapy with you, because I know you know so much more about it. I have a lot of experience with my squame patients. But what I've found is that very few patients really have problems. They tolerate cemiplimab very well. And I think that when you think about it, it's kind of scary, but for especially my patients who are in pretty good health, they tolerate it, they don't even know that they're on anything.—

--Now, the problem is there's that 0.1, 0.2, 0.3% chance that they can end up in the hospital or die. Now, most patients when you get to where you're wanting to use cemiplimab, they're willing to take those risks because they know they're in a bad spot. And so it's not that difficult to conversation. And some patients who have been on both, they were on the full strength Hedgehog versus cemiplimab, they're more happy on cemiplimab because it doesn't interfere with their life. They just have that small chance of having a devastating problem but that doesn't happen that often. And as you know, the oncologists and their staff are very good at identifying patients who have problems, and they get to these patients very quickly, and they monitor them very carefully.—

--So I really haven't had problems with cemiplimab and I certainly haven't had problems with Hedgehogs. Most of the time, my patients are very happy with both. But I will say that no treatment is often an indication. And what's very interesting is I can't predict what patients are

going to pick. Sometimes, I've gone into a room and said, "I've got this pill. I'd really like you to take this," and the family sits around and talks about it and says, "Well, we really want you to dig this out of their ear and get rid of it." And I'm like, "Okay, I wouldn't have picked that, but I guess we can do that."—

--It's kind of like then the nurse later is going, "Well, they didn't really like your sales pitch, did they?" But you can lean patients a certain way but eventually, the choice is, as you know, you make it together with the patient. So that's kind of how I go through it.

STEVEN CHEN, MD, MPH, FAAD: Let's say that you do end up deciding with your patient, obviously I think it's so important to highlight the fact that sometimes not doing anything is the right choice, but let's say that you do decide that you move forward with a systemic therapy. What's your end goal here? What do you tell your patient is kind of the long term plan? Are they on a Hedgehog inhibitor indefinitely? Are they on it until things get smaller and you restart it, which the natural inclination is that doesn't sound like a great idea. But I'm curious to hear what your usual counseling is for these patients.

SCOTT DINEHART, MD: What I tell them, and this is a little different, but what I tell them is that I want improvement. I have a pill that can shrink it, we can make it smaller. Once we have it smaller, we have a lot more options. And I never promise them that I can get rid of it or have a cure. But I do tell them that I just want them to know that I'm kind of greedy. That I like to get good results and I really like the good results, so there are times where I tend to push them a little bit. And I tell them that up front, that I want good results. I've had good results in the past and I think we can get good results.—

--I tell them that I'll work very hard for them. And when I take them on, it's like it's a personal thing for me. I want them to get as good of results as I can. Another tip that I have is that I tend to like to have patients to have someone with them, a lot of times they don't. But if they have

what I call a cheerleader, that makes a big difference. Because I kind of enlist that person and tell them that they're on our team also and that they are there to encourage the patient, make sure they're compliant with their medications, make sure that I hear about any adverse events or side effects.—

--Make sure that if there are problems, I know about them. But I find that I get better results, particularly in basal cell nevus syndrome patients, it's almost a must. If you don't have someone that's their cheerleader, is what I call it, you will not do as well and you will not get as good of results. But that's kind of my bargain with patient, again the two month rule, if they're not getting better in a couple of months we'll get off, but they never do because we're always getting good results. So it's not like I tell them they have to take it forever.—

--Now, the basal cell nevus syndrome patients, I kind of tell them that they have to take it forever. They're on a low dose, they're on L-carnitine. And they can have a month break, but I get nervous when patients take longer than a month because I worry about resistance, and I'm sure you do, also.

STEVEN CHEN, MD, MPH, FAAD: I do. And that's super helpful advice for counseling your patients when you're starting them on these drugs. I guess one other quick question for you, is insurance ever an issue? Do you ever run into a problem with getting it covered? And if so, any tips on how to ultimately get that medication for your patient?

SCOTT DINEHART, MD: We do. I have a large practice in Arkansas. We do a lot of biologics and it is a nightmare. You have to have people that you work with. The nice thing about Hedgehogs is that it's a one page form, you just have to check the box that they have advanced basal cell. And you have to put in an ICD-10 code and you sign it and that's pretty much it. In Arkansas, we have to write a little note if it's Medicaid, we have to kind of explain why we're

doing it. But it's generally always approved. The other thing that's nice is I do have patients that I've treated that my patients bring other patients in.—

--They find them in the homeless shelter or something. I've treated a few homeless patients and I've been able to get medication for them because the companies have a foundation that can provide that for them. And have samples of Hedgehog inhibitors that we can use. I don't think it's a big burden. I think it's much easier than the biologics. You don't have to go through so many hoops so I don't really see that as an impediment. I think people that say that haven't used them. It's like don't use that as your excuse, that's so easy, that can't be your excuse for not using Hedgehogs.—

--The other thing that I will say about patient progression is it's always hard to know when to stop. Because patients come in, if they're on lower doses it might take six or eight months or something, they come in and they're like, "Well, it's gone." Or even after a couple of months the family is like, "Oh, it's no longer bleeding and getting infected, it's gone." And you're like, "Well, it's not really gone." And then you're worried about stopping. Sometimes if you do think it's gone, get a biopsy, the patients don't want to necessarily get a biopsy.—

--So sometimes my deal with them is they'll say, "Why would I want a biopsy? It's gone." I go, "Well, I don't know if it's gone." And so what I tell them is, "Would you mind taking this another ten days a month, for another six or eight months?" And they go, "Well, no, not really because I'm not having any side effects." Okay, that's my bargain with them kind of. And so they're willing to not get the biopsy. And then sometimes, you get biopsies and that just helps you figure out what you have left, so that's kind of the way I do it.

STEVEN CHEN, MD, MPH, FAAD: Thank you, that's super helpful. Well, thank you so much for joining today, Dr. Dinehart. This has been such a broad sweeping kind of conversation on nonsurgical treatment of basal cell carcinoma. And obviously focused a lot on the Hedgehog

inhibitors but still thinking about the fact that we have topicals, we have radiation, we also have cemiplimab which is newly approved for this indication. But before we officially sign off, any other tips, anything else you'd like our listeners to know?

SCOTT DINEHART, MD: I think just the main ones that I've mentioned to you. The first one is that it's underutilized, Hedgehog inhibitors are underutilized. And also the fact that they should do this themselves. Don't send it to someone else, find that medically-inclined dermatologist or perhaps the high-performing midlevel that can do this in your practice, it's very rewarding. I would say that's really my biggest tip. The decreasing frequency of dosing, using L-carnitine. Cemiplimab, great for squames, we're still getting experience with basal cell. Those are probably the big messages. Find the cheerleader for your patient.

STEVEN CHEN, MD, MPH, FAAD: Wonderful. Well, as a medically-inclined dermatologist, I am embarrassed to say that I personally have not prescribed this nearly enough, so I look forward to using your tips in the future when I'm faced with a patient that might benefit from one of these many options that we've talked about. Dr. Dinehart, it's been a pleasure getting to chat with you today. And thank you to our listeners for tuning into another episode of *Dialogues in Dermatology*.

SCOTT DINEHART, MD: Thank you for having me.