What's New in the Management of High-Risk SCC
(Sponsored by Regeneron Pharmaceuticals)

Todd Mollet, MD, FACMS, interviewed by Carlos Garcia, MD, FAAD

BENJAMIN K. STOFF, MD, FAAD: From the American Academy of Dermatology, welcome to *Dialogues in Dermatology*. I am Dr. Ben Stoff, Editor-in-Chief. Thanks for tuning in.

BENJAMIN K. STOFF, MD, FAAD: This episode has been sponsored by Regeneron Pharmaceuticals. The American Academy of Dermatology retains control over the episode content and interview participant selection.

CARLOS GARCIA, MD, FAAD: Welcome to another edition of *Dialogues in Dermatology*. I am Carlos Garcia, from Oklahoma City. It is a real pleasure to have a dialogue about "What is New in the Management of High-Risk Squamous Cell Carcinoma," sponsored by Regeneron Pharmaceuticals. Today, I have the privilege of interviewing Dr. Todd Mollet, from Oklahoma City. Dr. Mollet is a board certified dermatologist and a fellowship-trained Mohs surgeon in private practice. Todd, thank you very much for taking the time to talk to us about this important topic.

TODD MOLLET, MD, FACMS: Dr. Garcia, thank you for inviting me to speak on this interesting subject today.

CARLOS GARCIA, MD, FAAD: Well, Todd, we all deal with patients with squamous cell carcinoma. That's an everyday experience for all of us dermatologists. So we happen to be familiar with the diagnostic and therapeutic options recommended by the experts. However, as you well know, not all the squamous cell carcinomas were created equal. Some can be very aggressive and devastating for our patients. So why don't you start by telling us, what kind of squamous cell carcinomas should we worry about?

TODD MOLLET, MD, FACMS: Like most dermatologists know, squamous cell carcinoma actually has as many deaths in the United States per year as melanoma, if not more. Fewer squamous cell carcinomas metastasize and kill patients but since there is such a higher number of squamous cell carcinomas, the total number of deaths is equivalent or even more than melanoma.—

--In my practice, I try to use the Brigham and Women's criteria for risk-stratifying squamous cell carcinoma. I think it's a very easy staging tool to remember. I think the AJCC 8 is a good staging tool, as well, but it's much more difficult to remember off the top of your head in a busy practice. So the four criteria that Brigham and Women's uses that I think about for high-risk squamous cell carcinoma are, number one, I look at the tumor.—

--If it's greater than 2 cm., then I'm a little bit concerned with it. If it has poor differentiation, also concerning. The third criteria is if it has perineural invasion of greater than 0.1 mm. And the last thing that I'm thinking about, especially whenever we're Mohs surgeons looking at the microscope, we can determine if the tumors are invading beyond the fat.—

--So I'm always thinking about those four criteria whenever I'm taking care of a squamous cell carcinoma. I'm always concerned if there's one of those criteria but if there's two, three, or four, I'm even more concerned with that patient's particular cancer.

CARLOS GARCIA, MD, FAAD: Very well, but we are sometimes in a gray zone because we have this high-risk tumor and we try to treat it, preferably with surgery and margin control. Sometimes, if the patients are poor surgical candidates, we may elect radiation. But in spite of treatment, sometimes the patients surprise you with a bad outcome with metastasis, local, regional involvement, etc. So is there anything new in terms of prognosticating these cases that otherwise for many, many years were just bad surprises for us?

TODD MOLLET, MD, FACMS: The newest thing over the last few years is the gene expression profiles. The patients with one or more of the Brigham and Women's criteria I just talked about, I consider ordering that test for. So as most people know, it's a 40 gene test that they take the formalin-embedded tissue from a biopsy and they test those 40 genes. And then it spits out a number that gives us an idea of the risk of that particular cancer.—

--So that test has three different classes. If it's a class 1, then I'm not as concerned about that patients' squamous cell carcinoma. That being said, I have had this study for patients that ended up being a class 1 and metastasized later on. So just because it's a class 1 does not mean the cancer absolutely will not spread. If you look at the percentages, about 7 to 10 percent of the class 1's for that genetic test can metastasize.—

--The other two classes, 2A and 2B, if you order the test and it comes back as a class 2A, the chance for metastasis is quite a bit higher, it's about 20 percent. And then if it comes back as a class 2B, then the risk for metastasis is over 50 percent. So I think combining the simple Brigham and Women's staging with that gene expression profile test, it does help us risk stratify our patients and figure out which ones are more likely to metastasize.—

--Again, it's not a perfect test because there still are patients where they may be a Brigham and Women's 1 or T1A or T2A, with a class 1 gene expression profile still can metastasize. But I think we'll catch more of these high-risk patients whenever we combine those two items. I know in melanoma, the gene expression profile as of now includes the clinical factors, which right now for squamous cell carcinoma if you order this test, it only includes the genetic factors.—

--But eventually, I think it will be combined where we have a combination of some sort of staging clinically, combined with the genetic profile of the tumor, we'll be able to follow those patients a little bit closer or maybe not as close, depending on what we find out from that combination of their staging, plus their genetic profile.

CARLOS GARCIA, MD, FAAD: Just for us to understand a little better, we have this clinical suspicion of a high-risk squame based on the factors of high risk, either clinical or histopathological. And then in those cases, you order this test that will give us a genetic profile of the tumor and predict, pretty good actually prediction, of the chances of metastasis. What do we do then? Is there any difference in how you work them up, how you treat them? Tell us more about this.

TODD MOLLET, MD, FACMS: That's the difficult question with this, is we should never order a test if it's not going to help us make clinical decisions for our patients. So I don't think there's a blanket approach for the test results and the clinical results. I do think if a patient comes back as a class 2A and they have a Brigham and Women's stage T2B, that particular patient has at least a 20 percent risk for metastases.—

--So number one, I'm going to be following that patient much more closely, probably seeing them every three months either in my practice or if I get a referral from a general dermatologist, having them follow up with that dermatologist every three months. Examining the tumor site, also their lymph node basin. We need to be checking lymph nodes on all of these patients. I would even say the low risk patients, we need to be checking the lymph nodes, but absolutely need to be checking lymph nodes on these patients with the higher risk profiles.—

--There is an argument for checking some imaging on these patients. So I know at meetings, we talk about ultrasound, or CT scan, or PET scan, or MRI. I think most people are using CT scans to watch these patients. There's a lot of user error involved with ultrasound. So I think at some academic institutions, ultrasound is probably the way to go to monitor the lymph nodes in these patients with higher risk genetic profiles and higher stages.—

--But I think for most people, probably CT scans are the best way to find tumors that have spread to lymph nodes or distant sites. I don't have, like I said, a blanket approach for these

patients but if I do decide a tumor is high-risk in a particular patient, I do like to get a baseline CT scan. Since most metastases or recurrences in these patients happen in the first two years, almost all in the first five years, but definitely in the first two years, I consider getting a biannual CT scan in these patients for a year or two.—

--Again, I don't have a blanket approach. There's no guidelines on this or any strong guidelines on this at this point. So you could argue against or for CT scans. But there are some studies that show if a patient has a single lymph node metastasis versus multiple lymph node metastases, the patients that have the single lymph node metastasis do better with treatment, because you're obviously treating their cancer earlier, before it has a chance to go to another node or to distant sites. I think that these CT scans or ultrasounds can help detect progressive disease a little bit faster than just clinical exam alone.

CARLOS GARCIA, MD, FAAD: That is very, very correct. But there are some questions about how to do this, Todd. For example, you and your partner are fully dedicated to skin cancer and Mohs surgery, whereas many of us are doing part-time Mohs surgery and doing general derm. So my question is, do you order the CT scan? And do you order it with or without contrast? Or is it valid for some of us to recur to the referral to an oncologist to help us with the imaging study? What is your approach?

TODD MOLLET, MD, FACMS: I think, especially for dermatologists, general dermatologists who are taking care of psoriasis, eczema, skin cancer all at the same time, I like to partner with an oncologist and I will often refer these patients. Most of my patients who I think need imaging I refer out to oncology and they do the workup for me. Some Mohs surgeons and dermatologists do that themselves, since I'm removing cancers all day and that's what I'm best at, I'm often referring to an oncologist to help me with the workup and the surveillance of these patients.

CARLOS GARCIA, MD, FAAD: That's what I do also, so I think it's important to emphasize that. Let's go to treatment. What is new in terms of local and distant treatments, surgical, nonsurgical, systemic? What can you tell us about therapy?

TODD MOLLET, MD, FACMS: In terms of treatment, the main principle of treating squamous cell carcinoma hasn't changed. The most important treatment is to get the cancer out and to obtain clear margins. I think the new treatments are when should we consider doing immune checkpoint inhibitor therapy, like the PD-1 inhibitors, when should we be doing adjuvant radiation therapy. So patients that are nontransplant patients, if we can't get their cancer out completely with surgery or they're a nonsurgical candidate, I do think we need to be considering the PD-1 inhibitors.—

--Most of these high-risk squamous cell carcinomas have increased PD-1 ligand. So it makes sense that the PD-1 inhibitors can be helpful in these patients. The other modality that we need to consider for these patients is radiation. This has been something that since I've been a resident, fellow, and acting Mohs surgeon, I've been trying to find new information on when should I radiate my patients and when should I not.—

--I still don't think there's a clearcut answer for adjuvant radiation in patients. I would say if the patient comes in, I can't get out their cancer completely with Mohs surgery, obviously radiation is an option at that point. PD-1 inhibitors are an option at that point. I think where people are not sure on what to do is if we get clear margins on a patient and they have a lot of these high-risk factors, if they have a 20 percent risk for mets, should we radiate those patients.—

--I do consider radiation on those patients. I think a lot of Mohs surgeons are with this new information, knowing that a particular cancer has a 20 percent risk for mets or a 50 percent risk for mets. There is no clearcut answer on if that is effective. So most of us know that if you send a patient for radiation evaluation, they're probably going to get radiation. So I think before we

decide on referring a patient for radiation, we and the patient need to decide if that's something they want to do and if they need. Because if they end up at the radiation doctor's office, they're most likely going to get radiation.

CARLOS GARCIA, MD, FAAD: Besides the radiation and anti-PDL-1, is there anything on the horizon or in practice right now to help these patients?

TODD MOLLET, MD, FACMS: This relates a little bit to the PD-1 inhibitors. In melanoma patients, they are treating patients with PD-1 inhibitors prior to surgery and those patients are doing better than patients who have surgery first and then the PD-1 inhibitors later. We don't know quite yet but that may be an effective way of treating patients with squamous cell carcinoma. So if we have a patient that comes back with a class 2B squamous cell carcinoma and it's 4 centimeters on their cheek, should we be doing PD-1 inhibitors prior to surgery? We don't know that yet but those patients, if you extrapolate the melanoma experience to squamous cell carcinoma, the patients with these higher risk cancers may do better than the patients that do not have the PD-1 inhibitors prior to surgery.—

--Other than those two things, obviously radiation is an old treatment. PD-1 inhibitors are relatively new. There's nothing that I am aware of for squamous cell carcinoma that's new.

CARLOS GARCIA, MD, FAAD: Now kind of finishing our interview, can you tell us something about prevention? Where are we in trying to prevent these tumors to occur in our patients?

TODD MOLLET, MD, FACMS: In terms of prevention, one thing that we had been using for a long time that is still effective is acitretin. The main thing with acitretin obviously are the side effects with acitretin, so it's difficult to keep patients on acitretin for a long period of time. The other issue with acitretin is cost. Acitretin, as most of us know, is an expensive treatment in the

United States. There are some pharmacies now that only do about a 10 to 15 percent markup on acitretin.—

--I can't specifically say names of individual businesses on here, but there are some pharmacies that you can get acitretin for $50 a month now, versus hundreds of dollars a month. So I think that is something that we should be considering. One thing with acitretin that is important to note is it helps prevent new cancers but it does not help prevent a recurrence or a previously treated cancer from metastasizing.—

--So it is proven to help prevent new formation of cancers but not proven to help prevent recurrence or metastasis of a previously treated cancer. The other new thing that I have seen for squamous cell carcinoma, a lot of us recommend niacinamide for our patients, usually 500 mg twice a day for patients who have quite a few squamous cell carcinomas or basal cell carcinomas. We're not sure at this point after a recent study if niacinamide is effective at preventing squamous cell carcinomas in transplant patients.—

--The study that previously came out about that was a little bit underpowered, in my opinion. So I am still recommending niacinamide for my transplant patients and also for my other patients who develop multiple squamous cell carcinomas per year. To my knowledge, there's very few side effects with niacinamide so I don't see the harm in doing something that some studies show does help prevent these skin cancers.

CARLOS GARCIA, MD, FAAD: Well, Todd, thank you very much for this entertaining and informative interview. I am sure that our audience enjoyed it and learned.

TODD MOLLET, MD, FACMS: Thanks again for inviting me to the interview, Dr. Garcia. Hopefully the audience learned something new today and I wish everybody well in treating their complicated squamous cell carcinoma patients.

CARLOS GARCIA, MD, FAAD: Well, friends, this was another edition of *Dialogues in Dermatology*. I am Carlos Garcia, from Oklahoma City. It was a real pleasure and privilege talking to Dr. Todd Mollet about "What is New in the Management of High-Risk Squamous Cell Carcinoma." Thank you.

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