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Selecting the RIGHT Patient for Systemic Therapy in cSCC: A Care Team Forum

Announcer:
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Dr. Schmults:
Hello, and welcome to “Selecting the Right Patient for Systemic Therapy in Cutaneous Squamous Cell Carcinoma,” the second of a 2-part care team forum. I’m Dr. Chrys Schmults, Director of Mohs and Dermatologic Surgery at Brigham and Women’s Hospital and Associate Professor of Dermatology at Harvard Medical School.

I'm once again joined by my colleagues Dr. Omid Hamid, Chief of Translational Research and Immunotherapy, Director of Melanoma Therapeutics, and a practicing medical oncologist at the Angeles Clinic and Research Institute in Los Angeles, and Dr. Anokhi Jambusaria, a practicing dermatologist from the Dell Seton Medical Center at the University of Texas. Jim and his wife Joyce are joining us again. Jim is both a patient of mine as well as a cutaneous squamous cell carcinoma survivor. He shared his experiences with us in the first part of this series, and we're glad to have him back again for this one. Welcome to you all.

So, to recap, cutaneous squamous cell carcinoma is a very common form of skin cancer, about a million cases per year in the United States. It is generally highly curable. The surgical cure rates can be as high as 99% for your average case, but there is a small subset of patients, approximately 2–3%, who can develop metastasis and approximately 1% who even can go on to die from disease. We now have our first FDA-approved drug to combat patients with these advanced tumors. It is a PD-1 inhibitor called cemiplimab, and trials to date with this medication have shown about a 50% overall response rate. And the safety profile has been consistent with other PD-1 inhibitors, so it is quite a well-tolerated medication, which is particularly helpful in our patient population which tends to be elderly and frail.

Jim, can you please recap your experience with cutaneous squamous cell carcinoma?

Jim:
Sure. Back in 2016, I found a growth on my neck, had it checked out, and come to find out that it was cancerous, had it removed and went on chemotherapy and treatment. That didn't work well, and I was given the opportunity to try—to go on the clinical trial, which in my case turned out to be very successful. I'm very happy with how things turned out for me.

Dr. Schmults:
Thank you. And 2 years prior to the neck mass you had had your original squamous cell cancer on the cheek, which was presumably the tumor that led to the metastasis.

Jim:
Correct. I had like a pimple, what I thought was a pimple, and it turned out to be a little bit more serious than that, but that was removed, and then for 2 years I had no idea that anything had continued or if they were even related, but pretty much that was how it went.

Dr. Schmults:
All right. So, talking about the cemiplimab trial, in any type of trial, clinical trial, there are inclusion/exclusion criteria. Dr. Jambusaria, could you tell us a little bit about how you think those inclusion/exclusion criteria may or may not be applied to the current population of patients where we

might like to use a PD-1 inhibitor?

Dr. Jambusaria:
Absolutely. So, for the clinical trial, the inclusion criteria was that you had had to have a histologically confirmed cutaneous squamous cell carcinoma that could be measured by RECIST criteria, you had to be pretty healthy and have good liver, renal and bone marrow function, and then the most important part was that you had to be a poor surgical candidate, so you had to have either metastatic disease, have multiple recurrences in the same location, have significant local invasion or have significant morbidity associated with surgery, as was discussed previously. You were excluded from the trial if you had a history of solid organ transplantation or were on immunomodulators, if you had some type of autoimmune disease, such as inflammatory bowel disease or lupus, that required immunosuppression, if you were on continuous steroids for any reason or if you had a history of infections, such as HIV or hepatitis.

In the real world I think that these are generally good guidelines in terms of when you think about which patients you want to consider cemiplimab or a PD-1 inhibitor for. However, as with all clinical trials, clinical trials are going to be designed with a very narrow scope, and so some of these exclusion criteria I would actually consider putting one of these patients on a PD-1 inhibitor. So, for example, if they have chronic lymphocytic leukemia, I think that that would be a discussion where I would consider that, or even if they had inflammatory bowel disease and systemic lupus, even if they were on an immunosuppression, I think that would be a discussion to be had of their risk of their lupus flaring versus the risk of their advanced or metastatic squamous cell carcinoma progressing, and so I feel like the exclusion criteria would not necessarily apply as much to me in this population, but certainly, the inclusion criteria, that is kind of how I think about who might be a good candidate for this medicine.

Dr. Schmults:
Dr. Hamid, in your practice, how do you determine who gets systemic immunotherapy?

Dr. Hamid:
Right. For me, I can think back to my first patient where I thought cemiplimab was an opportunity, and that is a patient who had a recurrent cutaneous squamous cell carcinoma in an area around the orbit where there was concern about nerve invasion where radiation and surgery would probably not render them free of disease; there would be microscopic remain. And also, those options would have a contraindication, whether it would be disfiguring with a loss of an eye or that it would be in an area where radiation may cause visual field defects, and this is a patient where we discuss initially bringing on a PD-1 inhibitor to evaluate benefit and go forward.

Dr. Schmults:

Dr. Jambusaria, how about you? Tell us a little bit about your early patients on cemiplimab?

Dr. Jambusaria:
Yes, so the first patient that I had a discussion with about putting on cemiplimab was a younger woman who had metastatic squamous cell to the inguinal nodes, actually, and surgery would be very difficult, very morbid procedure to remove the primary tumor—it was a very large tumor—and ultimately, the patient decided that surgery was not really a good option for her, that she wasn't—didn't want to undergo surgery, and so ultimately, the decision was made to put her on a PD-1 inhibitor.

Dr. Schmults:
Similarly, my first patient who we enrolled in the cemiplimab trial was a person in her early 90s when she started the trial, and she was able to tolerate the drug for over a year before she finally progressed, but she went on trial because she had a large tumor just right over her joint space of her knee, and it was felt that to try to remove the tumor we'd be into the joint space, she'd probably end up having infection or complications of that joint space, which in somebody her age, if they lose their ability to ambulate well, is really going to be probably even a potential morbidity risk when someone in their 90s is immobilized. And then also she had diffuse squamous cell carcinomas to a lesser degree over both of her legs, and so the hope was that we could bring her legs overall into much better condition. The drug did work for a time on the largest tumor, but it had intermediate effects on her background field cancerization.

Dr. Jambusaria, do you think about using immunotherapy, systemic immunotherapy, to control field cancerization?

Dr. Jambusaria:
Yes. Traditionally, that has kind of not been the mainstay of treatment. We have lots of different treatment options for field cancerization, which mostly include topical chemotherapy, other topical creams or light therapy like photodynamic therapy. From some of the anecdotal evidence in the clinical trials, the medication was not as effective in helping with background field cancerization as the investigators would have hoped, and so I think right now the jury is out there as to whether or not this medicine should be utilized for use for background field cancerization.

Dr. Schmults:
So we know from the cemiplimab trial that there is an overall response rate of about 50%, and so half of our patients will be responders, half won't be. Could you just talk a little bit, Dr. Hamid, about steps for nonresponders? What do you do for that 50% of patients who don't respond?

Dr. Hamid:

So, for those 50%, I would look to see if there is another type of immunotherapeutic protocol to move on to. There is great data about oncolytics, which are injectables directly into the tumor that can stimulate an immune response, and those are being looked at in patients who don't get an initial single-agent response going into combination. As I have mentioned, PD-1 is not the only checkpoint inhibitor. There are checkpoint stimulators and checkpoint inhibitors that are coming out in single-agent form or in combinations, and that is where I would look to take these patients as we've seen that we can initiate a response even after progression. There is data coming forth from radiation, the ability for radiation to stimulate the induction of antigen and antigen released to reignite the immune system, so I would say I would go looking for what has been successful in other immunogenic tumors and move them forward.

Dr. Schmults:
Dr. Jambusaria, is there any way to select patients in advance who are more or less likely to respond to immunotherapy?

Dr. Jambusaria:
I don't think we really know the answer to that just yet. I think from the clinical trial there were no predictive markers that would help differentiate responders from nonresponders, but there is a lot of current research and studies going on to look at and to address that very question, and so, hopefully in the next few years we'll have an answer to that so we can kind of try to pick the right patients who will then receive the maximal benefit from the medication.

Dr. Schmults:
For those patients who do respond, the fortunate 50%, the response—we still haven't seen the median response that is just beginning to be plateauing, and so we're hopeful that most of the patients who do achieve a response, especially those people who achieve a complete response, are going to be able to maintain that response. We talked about in the last segment we don't quite have that data yet. We're only out to about a year, so 5-year survival hasn't been reported yet.
Dr. Hamid, could you talk a little bit about the average time to response? How quickly are you going to know if somebody is a responder or nonresponder?

Dr. Hamid:
Traditionally, the responses in this tumor type have been rather early, somewhere between the middle of after 1 month to 2 months, and you'll see a significant proportion of patients have that, but I would hold steady for anyone who looks like they are having a disease control at the onset and moving forward. As we've seen with this tumor and other tumors, that you can initially begin with a stability of response that then becomes a more durable and deeper response.

Dr. Schmults:

Jim, could you tell us a little bit about when you first felt that you were responding to therapy?

Jim:
I really think it was pretty quick in the process. I mean, Joyce as the caregiver would have seen it better than me, but I would think maybe 3, 4—3 to 4 weeks. I felt that it, you know, was getting a positive response, but again, Joyce is the one that was kind of...

Joyce:
I would say what I was seeing initially… And of course you're so focused on looking for these changes because it was so visual. What we saw was or what I saw was changes. It was like I couldn't say they were getting smaller, you know, but I didn't see new ones, and I saw changes, you know, like… But I didn't know what that meant. You know, I'd see like sort of maybe like the tumor would develop a core, and I'd see like white spots, and again, I didn't know what does that mean. Does that mean that it's... And as it turned out, it turned into disease regression. It was just... But that's how it started. And then they would... Each time they would just be, you know, smaller, and I'd be like, "This is definitely smaller. This is definitely..." You know, and then they just sort of melted away.

Dr. Schmults:
Dr. Hamid, what advice would you give clinicians treating patients today with advanced cutaneous squamous cell?

Dr. Hamid:
I think it's important to evaluate this data that has come up and this therapeutic option. Just like I have in my clinic, it's become a multidisciplinary experience for every patient where we involve radiation and our dermatological partners. I think it's easier to recommend this therapy given that this class of drugs has clearly been in the clinic for other solid tumors, but the belief comes from treating a patient and seeing the benefits. What I would say to patients and physicians alike, it's a very tolerable regimen. The side effects are rather benign and insidious. We have to look out for them. And educating your patients about the immune-related adverse events is important to identify and treat them quickly so that we can get maximal benefit.

Dr. Schmults:
NCCN guidelines have recently been updated to reflect the data of the cemiplimab trial to let clinicians know that immunotherapy is an option for patients with unresectable disease or metastatic disease.

Jim, from your perspective, what would you advise doctors treating patients like you?

Jim:
Well, I think I was very fortunate at Dana-Farber. They kept me very well-informed. You know, if they

wanted to know of any changes, GI problems, rashes, itchiness, anything at all, and they also, again, said things might get a little worse before they get better, so I was handled very well, and I think, you know, if you just tell a patient that there might be some side effects but what they could be, at least you're aware of it, because if you don't know that that's a possibility, you might have a tendency to think that there is something else going on, but I was very happy with the way that things were handled for me. There were no surprises I guess is what I'm, you know, where I'm going with that.

Dr. Schmults:
So these photographs here illustrate a patient of mine with cutaneous lymphocytic leukemia, CLL, for whom I wished I would have had cemiplimab available at the time. This patient had, as you can see on the left, in 2009 a large, deeply invasive squamous cell carcinoma, and that tumor was successfully excised by a Mohs surgery with a craniectomy centrally for an area of superficial bone invasion, and it never recurred.

The central photos from November 2014 show that resected surgical site on the far right, but then, unfortunately, he developed multiple other tumors on the mid left side of his scalp. Particularly, the one with the blue circle shows frank bone invasion, gross bone invasion, and that tumor, unfortunately, was not able to be completely resected. Intraoperatively when the craniectomy was attempted, the patient became hypotensive, and so complete resection of that bony area was not able to be undertaken. And you can see that he very rapidly progressed so that it was as if we had done no surgery at all on him by about 5 months later, and this patient ultimately succumbed to his disease with extensive dural extension as he suffered more bone erosion from the tumor.

The story of this next patient highlights some of the real clinical dilemmas that we face in this disease, and a fairly typical story. This is a renal transplant patient who had a large squamous cell carcinoma of his central cheek about a decade ago, and over that decade he underwent several different surgeries, first by a plastic surgeon and then by myself, in total about 5 different surgeries culminating with loss of his eye, as you can see here in the photograph on the right, and a free flap. And despite these various surgical attempts and 2 courses of radiation, the tumor continued to recur, and you can see several different erosions around the surgical site as well as an area of in-transit metastasis below his ear and a new erosion on his nasal mucosa. So it's clear in a patient like this that our attempts at surgery and radiation have failed, and this is certainly someone who falls into the unresectable category. I think had we had cemiplimab available, we probably would not have undertaken his final surgery, which led to loss of the eye, because at that point he had already failed several surgical attempts and the 2 courses of radiation, and the odds of really controlling this disease really start to lessen with this kind of a clinical picture, but his situation is increasingly complicated by him being a renal transplant patient.

So he did have a disease-free interval after his last major surgery before these erosions appeared, and we briefly thought about PD-1 therapy at that point in time, but given in the data to date there is about a 50% chance of organ rejection, we opted not to do that in an adjuvant setting where he was disease-free for the moment. However, when he developed these erosions, we felt that finally there was no other really good option for him, and he was willing to lose his kidney and potentially go on dialysis in order to treat this tumor. So, not an easy decision, but that was the decision that he made. We initiated PD-1 therapy with pembrolizumab, and he had a complete response and the tumors all regressed.

Unfortunately, just about the time that he had his complete response, he did start to have rejection of his kidney, but this was successfully treated, and his creatinine came back close to baseline, and he is now stable from a renal function point of view and he is no longer on the pembrolizumab, but he has remained disease-free for a total of about 5 or 6 months now, so we're hopeful that maybe he could be one of our complete responders, but time will tell.

And then this is Jim's own photographs here, and you can see on the left how fulminant this disease can be, and I can only imagine how scary to see these tumors grow over the span of a few months.

Jim:
Yep, just about a month, yeah, month and a half maybe, yeah.

Dr. Schmults:
And then the photo on the right is after about 8 months of cemiplimab therapy with complete resolution of the disease.

Dr. Jambusaria, could you give us a little bit of your perspective on patients, particularly transplant patients, and how we might approach them now that we have systemic therapy?

Dr. Jambusaria:
Absolutely. This comes up a lot. I do a lot of transplant dermatology, and so I see a lot of transplant patients. Our transplant patients often times are the ones who get kind of the more aggressive squamous cell cancers and are more likely to have metastatic squamous cell cancer, and so this is a clinical scenario that does not come up infrequently in our patients. And as previously discussed, PD-1 inhibitors, because they activate the immune system, basically there is a risk to graft function if they are put on these medicines. For most organ transplant recipients, probably PD-1 inhibitor therapy is not a great option for them, so heart transplants, lung transplants, liver transplants. Because the risk of rejection is so high and you can't live without these organs, it's probably not a great option for them. For renal transplant recipients, however, because they do have that option to go back on dialysis, it is something that probably is worth considering, especially if the patient is willing to go back on dialysis.

There is a lot of research that is going to happen now that the drug is approved—testing these medicines in this specific population to see what is the true risk of transplant rejection, are there things that can be done to prevent it. There are case reports in the literature of patients who have lost their graft on PD-1 inhibitor therapy, and there are also case reports of people who have been able to have graft preservation with pulsed prednisone as well, so I think that the jury is out there. I have a patient who next week is going to be starting this who has metastatic squamous cell and is a renal transplant recipient who is willing to go back on dialysis. And as long as patients are well-informed and are willing to kind of consider that option, I think it is worth discussing.

Dr. Schmults:
So, to expand a little bit more on this, we often talk about shared decision-making in the context of improving patient outcomes in cancer care. And this is for everyone here on our panel. Do you think that that is relevant here? Do you think that clinicians are using shared decision-making with our cutaneous squamous cell carcinoma patients?

Dr. Hamid:
Absolutely. I think we're sharing the decisions between our own colleagues and we are adequately educating our patients to be on the level to really be involved in their care and their decision-making process.

Dr. Jambusaria:
Yes, I totally agree with that.

Dr. Schmults:
Do you work with tumor boards? How does that work in terms of your colleagues? And then how do you bring that back to patients? There is something called the three-talk Elwyn model that emphasizes that it might take more than one conversation with a patient. Patients need to have their options presented; then, perhaps, even at a different time have another conversation about alternatives and weighing out those different options before they finally come to a consensus.

Dr. Jambusaria:
At our institution we do have a multidisciplinary tumor board that meets on a regular basis, and if I have a patient who I feel like needs to be considered for kind of multidisciplinary consultation, we usually discuss it at the visit or at the time of their diagnosis that this is my plan in terms of what I'm going to be doing, that I'm going to be taking their case to tumor board and will call them whenever I have kind of a consensus opinion from the tumor board. Then their case is presented at tumor board, and I usually follow up with them the same day to let them know what was discussed, but then I also bring them back in the following week to kind of have a face-to-face discussion with the patient, and I think that is really

important—like you mentioned, letting the patient hear the same message a couple of times—and also, I think, giving them time to process all their options and kind of weigh all their options. And usually, by that time we're able to come to some kind of consensus as to how is the best way to move forward.

Dr. Schmults:
Jim, how were your treatment options discussed with you?

Jim:
Okay, at Dana-Farber I felt they were handled excellently. I met with the team that consisted of a surgeon, a radiologist, oncologist radiology person, as well as the oncologist, and we met and we discussed the different options, and it was fully explained to me the best way they could do it, what they felt it was, and I bought in on that based upon because I had different theories and I know that they were all looking out for my good, but they were very informative, and I found that very helpful. Even as I went down the road and kind of hit a bump in the road when it started to metastasize, I was still told that there were options, we'll work very closely with you, so I think that overall I was very satisfied with the whole treatment that I got from Dana-Farber and the whole—the way that the message was delivered and how I was going to be treated. I found that to be a big, a big asset.

Dr. Schmults:
One other question for the group. If there is a lack of consensus at tumor board or among the different colleagues involved on the team, how does that get resolved at your institutions?

Dr. Hamid:
At our tumor boards, if there is a lack of consensus, then we discuss that with the patient and give them the opportunity to be seen in consultation by the differing opinion. It might not actually be a dissenting opinion. It might just be a differing opinion on how you would stagger the therapies. And that is absolutely important to be able to provide to patients.

Dr. Schmults:
Jim, it sounds like in your experience your clinicians were pretty unified in their thoughts at different points in time.

Jim:
Yes.

Dr. Schmults:
But how do you think you would have felt if one doctor had one idea for you and another felt like there was a different route that was maybe better?

Jim:
Well, I think the fact… Even just an open discussion about it, you know, if somebody wasn't so much dissenting but they had a different opinion on it, it would be good to hear that, and I think that would have come out during our suggestions, so I don't think that's a bad thing. I think you've got to... If somebody feels strong enough about one thing and it has to do with, you know, how it's going to affect you, at least if they share that with you, I think that's a very good thing. I mean, it's just some more stuff that you've got to go through to make your decision, but I still think you need to know that. And like I said, I was very fortunate that the team met with me and they... You know, we talked about a few different options, but the consensus was right out of the gate that we—let's go with the surgical thing, and then we'll worry about step B, and then we'll worry about C and after that, but there was a game plan, and I was content with that. I was very content with that.

Dr. Schmults:
What we've just said about the importance of tumor boards is really wonderful, but there are people practicing out in the community who don't have ready access to a tumor board and they are forming their own teams as needed. What advice could you give to them, Dr. Hamid?

Dr. Hamid:
I would say that it is important to reach out to the colleagues that you utilize in that fashion and have phone calls and direct communication. It's also important to go back to the literature and discuss it with the patient and your colleagues in order to come to an informed decision. That may not have happened at one place at one time but is a dynamic process.

Dr. Schmults:
Dr. Hamid, could you talk a little bit about the data that is available about shared decision-making?

Dr. Hamid:
Yes. So, very early in my career I came to the realization that I was not involving the patients enough and educating them about their situation, about the therapies that they were getting and what to expect and what could be the next therapy afterwards, so we have gone out and sought those sites or those helpful places for our patients and made sure that we spend some time discussing with patients what they've heard and how they have taken that in, and if there is a lack of understanding, refreshing or having another visit before a treatment decision is made.

There are great resources to help bridge that communication divide. I use magazines that have been set for patients like CURE magazine or some support groups for certain tumor types, but I've also found that a nurse who has experience with similar patients is very helpful. And as I mentioned in the research program, our research nurses really help bridge that divide that works to help patients

understand what is going on and help physicians working as a mouthpiece for the patient, so saying something like, “You might not have heard,” or, “I’ve heard,” or, “This may not have come across appropriately.” So we do try and have those visits where the focus is on educating and understanding more. I’ve found that patients who are involved in their care have a better treatment course. They feel free to communicate toxicities. Let’s be honest. Some of these therapies can become severe, and if you catch them early, it’s much better for the patient.

Dr. Schmults:
I find that different patients really do react to information and want information in different ways. I have some patients as new consults who will just say, “Whatever you think, doc. What do you think I should do?” And whatever I recommend they really want to do that. I’ve had other patients come in often times because they have had experiences with different therapies already and they’ll have very clear ideas about what they will and won’t accept, and so they are setting some pretty structured boundaries for us to work within. And then, of course, you have patients in between, and so I find that you really have to adapt your style and your way of talking to people to suit those different situations while still trying to provide everybody with the basic information that you feel they need to make an informed choice.

That’s all we have for you today. Thank you for participating in this discussion. Please don’t forget to take the posttest and complete the evaluation to receive CME credit. And if you haven’t already, be sure to check out part 1 of this educational series where we all dive a bit deeper into the data behind new and emerging systemic therapies for cSCC. Once again, thank you for joining us in this care team forum.

Dr. Jambusaria:
Thank you.

Jim:
Thank you.

Joyce:
Thank you.

Dr. Hamid:
Thank you.

Announcer:
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