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cSCC Patient Clinic

Announcer:
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Dr. Schmults:
Hello, my name is Dr. Chrys Schmults, and I'm a dermatologic surgeon at Brigham and Women's Hospital in Boston. Today I'll be discussing 3 clinical case scenarios on cutaneous squamous cell carcinoma with my colleagues Dr. Anokhi Jambusaria, a dermatologist from the Austin Dell Medical School, and Dr. Omid Hamid, a medical oncologist from the Angeles Clinic in Los Angeles.

We'll begin with our patient Jersey. Jersey is an elderly retired teacher. She has a history of diffuse field cancerization consisting of multiple actinic keratoses and in situ squamous cell cancers on her lower legs. These have been monitored by her primary care doctor but have not been treated. Seven years ago she underwent knee replacement surgery. She is referred to you now due to the development of a

large, rapidly growing squamous cell cancer on her knee. She also has a history of atrial fibrillation for which she is on warfarin.

You can see her tumor pictured here, and you can see that this is an 8 cm tumor on her left knee and that she also has several smaller lesions on her lower legs. There is no evidence of lymph node involvement on her exam or on CT scan.

Biopsy confirms that this is an invasive, poorly differentiated squamous cell carcinoma extending 8.6 mm into the subcutaneous fat. There is perineural invasion of the nerves running within the subcutaneous fat, and the MRI shows that the tumor is abutting the joint space.

Given the below treatment options, which would you be most likely to consider for this patient? The correct answer is D) radiation and chemotherapy. Mohs surgery alone is unlikely to be effective for a tumor like this, mostly because of the difficulty in clearing the deep margin. In order to clear a tumor that is abutting joint space, the joint cavity would likely have to be opened, and in somebody this age, of advanced age with a knee replacement, there is a high likelihood that that joint space would become chronically infected, ultimately leading to a high risk of amputation, which is very hard for such an elderly patient to tolerate. The same holds true for answer B, which includes surgery, as well as C. So in this case we are really describing a patient who is inoperable.

So, how do we define someone who is a poor surgical candidate? Lots of different factors weigh in. Again, in this case, somebody's age. In a younger patient, they might be able to tolerate an amputation, in which case this would be an operable tumor. Comorbidities can factor in, but not particularly in this patient's case. We routinely treat patients who are on blood thinners and anticoagulants. In most dermatologic surgical scenarios we don't stop those treatments. Some very large tumors are able to be resected surgically, and so it is very important to get a surgical consultation before any patient is deemed surgically unresectable. The location and tumor depth can come into play, particularly with regard to location. If a patient is facing orbital exenteration and they don't have good vision in the other eye, that can put patients in a situation where they are facing a very different quality of life afterwards.

AJCC-8 staging has several features that upstage tumors to T3. These include thickness greater than 6 mm or extension beyond the subcutaneous fat—for example, into muscle or deeper fascial layers—clinical diameter of 4 cm or larger as in this current case, invasion of a nerve deeper than the skin or 0.1 mm in caliber, and minor shallow bone erosion. Any one of those features will upstage to T3.

Dr. Hamid, how would you have treated this patient with unresectable cutaneous squamous cell cancer in the pre-PD-1-inhibitor era?

Dr. Hamid:

Dr. Schmults, in the pre-PD-1-inhibitor era, there were a small number of options—of course, radiation locally to garner some control and regression, chemotherapy based on a platinum backbone would have been interesting in single-agent or combination chemotherapy along with radiation, and then EGFR inhibitors like cetuximab would have been an option in relation to the history of responses. Although, with chemo and EGFR inhibitors, what we had seen is responses that were short-lived and no clear survival benefit. These combinations would have been what would have been used at that point.

Dr. Schmults:
All right. And, Dr. Jambusaria, how would you approach treating this patient today?

Dr. Jambusaria:
Well, as discussed earlier, this patient is a poor surgical candidate, and we have limited radiation and chemotherapeutic options. Luckily for us, in 2018, we had approval of cemiplimab, which is a PD-1 inhibitor for the treatment of patients who had locally-advanced, unresectable, cutaneous squamous cell carcinoma who are not candidates for curative surgery or radiation or if they had metastatic disease. The response rate with cemiplimab is approximately 50%, which means that about half patients will actually not respond to treatment, and in these patients we may need to consider some experimental agents.

Here on the next slide are listed several agents, some as single agents and others as combination regimens that are currently being investigated. And if you have a patient that falls in this nonresponder arm who fails cemiplimab, I would encourage you to look at clinicaltrials.gov to see what trials are available in your area.

Dr. Schmults:
Great. It's so wonderful that we finally have an FDA-approved option for patients who are unresectable or metastatic.

Moving on to the next case, we have Cash. Cash is a patient who you began seeing for chronic lymphocytic leukemia approximately 2 years ago. He received chemoimmunotherapy with rituximab and CHOP and achieved complete remission 9 months ago. Prior to his CLL diagnosis, he had 5 squamous cell cancers removed over 5 years. In the 2 years since his CLL diagnosis, he has had 5 more squamous cell cancers. All have been low-stage tumors. He returns to you now concerned that he has a new squamous cell cancer. His physical examination shows this tumor on the upper trunk measuring 1.7 cm with no palpable axillary lymph nodes. On biopsy this is a squamous cell cancer with a depth of 3.3 mm confined to the dermis. It is moderately differentiated, and there is no evidence of perineural or vascular invasion.

Which of the following statements regarding the presence of multiple squamous cell cancers is most accurate? The correct answer is B) Patients with multiple lesions have a greater risk of recurrence.

Cutaneous squamous cell cancer is relatively unique in the cancer world because patients often have multiple different primary tumors over their lifetime. And patients who get multiple tumors, especially those who really have a significant problem with squamous cell cancer formation with more than 10 primary tumors over their lifetime, excluding in situ disease—so this is 10 dermally invasive squamous cell cancers—these patients have a 37% risk of local recurrence and a 20% risk of metastasis respectively, and this is much higher than the usual 1–4% risk of metastasis. Particularly, that 26% risk of metastasis is really something to think about in a patient who is having multiple tumors over and over again. They do stand a high chance of ultimately forming an aggressive one that has metastatic potential.

Dr. Jambusaria, what would be the best strategy for preventing formation of new squamous cell cancers in a patient like this with a history of forming multiple tumors?

Dr. Jambusaria:
As a dermatologist, I feel like I have multiple options in terms of what to consider for a particular patient like this. First-line I would consider oral nicotinamide at 500 mg twice a day. There is a randomized clinical trial that shows a 20–25% reduction in new skin cancer formation at 1 year. The other option I would consider is oral acitretin. There is a small randomized-controlled trial that also shows decreased squamous cell carcinoma formation in patients who develop multiple squamous cell carcinomas. If these 2 options fail, then I might consider referring the patient to my medical oncology colleagues for consideration of oral capecitabine.

Dr. Schmults:
Dr. Hamid, could you tell us a little more about oral capecitabine as prophylaxis against squamous cell cancer formation?

Dr. Hamid:
Sure, sure. Capecitabine is a prodrug that is converted enzymatically to its active metabolite. It was initially approved in 1998 for breast cancer and then subsequently for metastatic and primary colon cancer respectively. It was observed that in some of these breast cancer patients being treated with capecitabine, actinic keratosis became inflamed and some resolved. This observation is similar to topically applied 5FU, which is capecitabine. Now, oral, low-dose capecitabine has since been used for chemoprevention. It is typically administered in lower doses for 1 to 14 days of a 21-day treatment cycle, similarly to how it's given to other patients, and then cycles are repeated until disease progression for toxicity. Studies have shown this regimen to reduce reduction of both squamous cell

carcinomas and actinic keratosis. It is well tolerated by most patients, but treatment-limited side effects may be observed, and most commonly, side effects include fatigue, diarrhea, hand-foot syndrome, decreased blood counts, and oral ulcers.

Dr. Schmults:
Thank you. Since the majority of patients who form 10 or more squamous cell cancers are immunosuppressed, usually due to CLL or organ transplantation, are there any special considerations or difficulties using nicotinamide, acitretin or capecitabine in patients with a history of CLL or organ transplantation?

Dr. Jambusaria:
So, for nicotinamide and acitretin, there are few things that you should be aware of. Nicotinamide is excreted through the kidney, so you would need to make sure that the kidney function is normal prior to starting it. However, its safety has been described even in kidney transplant recipients as long as the creatinine is normal. And with acitretin as well, this is perfectly safe in transplant recipients or CLL recipients. Acitretin is not further immunosuppressive, and we would monitor kidney function as well as liver function and cholesterol on this medication.

Dr. Hamid:
And for oral capecitabine, patients should be screened for dihydropyrimidine dehydrogenase deficiency. If present, this may lead to severe toxicity. Additionally, renal function should be assessed before treatment because impaired function may contribute to development of severe side effects. We also do talk to the transplant physicians for a discussion about the opportunity to decrease immunosuppression.

Dr. Schmults:
Right. Decreasing immunosuppression or conversion to an mTOR-based regimen has been shown to really decrease squamous cell formation in our organ transplant population. Thank you.

So, switching gears to a related but slightly different topic, in this next slide we have a patient who has field cancerization. Dr. Jambusaria, could you define field cancerization for us and how it differs from patients who have multiple dermal squamous cell cancers?

Dr. Jambusaria:
Sure. So, field cancerization is defined as diffuse involvement with actinic keratosis or squamous cell carcinoma in situ with or without having a dermally invasive squamous cell carcinoma in a field. As you can see from the photograph here, this is a patient who has field cancerization. The red arrows correspond to multiple actinic keratoses, and the black circles respond to multiple squamous cell

carcinoma in situs. This is a patient who has a diffuse area of involvement, and that person is at high risk for the development of dermally invasive squamous cell carcinoma.

The treatment strategies for patients like these involve treating any dermally invasive squamous cell carcinomas as we normally would, ideally with Mohs surgery or complete peripheral—histologic peripheral margin assessment when possible and then targeting the actinic keratoses and squamous cell carcinoma with some type of field treatment. Common employed field treatments include topical 5-fluorouracil or PD, photodynamic therapy. These are patients where we would not consider PD-1 inhibitors given that the invasive squamous cell carcinomas are usually operable and that we have good options for the actinic keratoses and squamous cell carcinoma in situs with field therapy.

Dr. Schmults:
Thank you. So the goal of treating field cancerization is to treat this superficial epidermal field of abnormal cells in the hopes that we are going to decrease the number of dermal squamous cell cancers that form?
Dr. Jambusaria:
That is correct. So we know that patients who have field cancerization—we think that they have a higher risk of developing dermally invasive squamous cell carcinomas in the future, and as discussed previously, patients who develop 10 or more invasive squamous cell carcinomas have a higher risk of recurrence and metastases. So the idea is, by aggressively treating the field cancerization, we are hopefully decreasing their risk of developing invasive squamous cell carcinomas and ultimately decreasing their risk of recurrence and metastases.

Dr. Schmults:
Thank you, so hopefully putting them in a class where they'll never need a PD-1—anti-PD-1 drug.

Dr. Jambusaria:
Exactly.

Dr. Schmults:
Moving on to our final case, Loretta is a 63-year-old accountant referred to you for new skin lesions. Two years previously a cutaneous squamous cell cancer was removed from her ear via Mohs surgery. She reports it was the size of a walnut and invaded cartilage. Her ear was partially removed but looks otherwise normal on today's exam. In the past 3 months, a new lesion has appeared on her cheek, and she notes shortness of breath. She has a history of elevated cholesterol and is receiving hormone replacement therapy but is otherwise in good health. On her exam she has this 1.6 cm deep-seated nodule on her right cheek. She also has multiple similar lesions, 1 to 2 cm on her right neck, and she has wheezing noted in her right lower lung field. A CT scan of the chest reveals multiple opacities,

including a 5 cm mass in the right lower lobe. Biopsies confirm that squamous cell carcinoma is present in her cheek, neck and lung, and a diagnosis of metastatic squamous cell carcinoma is made with the primary lesion presumed to be the large squamous cell cancer that had been removed from her ear 2 years previously.

Given this patient's presentation, which of the following members of the multidisciplinary team will be most likely to lead her treatment? The correct answer is a dermatologist and/or medical oncologist, depending on the treatment center.

Multidisciplinary collaboration is important in almost all cancer therapy, and particularly so in cutaneous squamous cell carcinoma. The dermatologist is often the first person to diagnose a tumor, and often, as we have described, this very well may not be the first squamous cell cancer that the patient has had. A pathologist is very helpful in the staging of the tumor and telling us about prognostic features which may impact the risk of recurrence or metastasis. Radiologists also help us with staging to evaluate lymph nodes and rule out distant metastasis. A surgical opinion either via Mohs surgery or head and neck or surgical oncology is required to determine whether or not a tumor is operable. And then radiation oncologists often become involved once a clear margin has been achieved in the adjuvant setting for particularly aggressive tumors or if a tumor is not able to be fully resected.

Medical oncologists, and in Europe, dermato-oncologists, become involved generally at the unresectable stage or when metastases have developed, and particularly now that we have a treatment for patients who are unresectable or who have distant organ metastases, systemic therapy is going to come more and more into play for patients with such advanced disease. In most US centers, because cemiplimab is an intravenous infusion therapy, medical oncologists are likely to lead that portion of the management. However, at some centers dermatologists are also able to administer such intravenous therapies to their patients, and in these cases, dermatologists and medical oncologists will work closely together to monitor for side effects.

There is also a strong role for the patient to be involved in decision-making, particularly for advanced disease, where patients are trying to weigh the options of surgery versus systemic therapy. And particularly in cases where surgery may have a large impact on a patient's long-term quality of life and the likelihood of cure is questionable, that is when a patient really needs to be very well-informed and think about the different options at their disposal and how to weigh the risks of, perhaps, a slightly higher cure rate with surgery but with a potential higher morbidity versus an approximate 50% chance of controlling their disease for some time on anti-PD-1 therapy.

Dr. Hamid, how would you have managed this patient with metastatic cutaneous squamous cell carcinoma?

Dr. Hamid:
Dr. Schmults, prior to the PD-1 era, we would have had an extensive discussion in relation to chemotherapy with a platinum-based agent, also EGFR inhibitors like cetuximab; but now, clearly, first-line therapy discussions, they center around PD-1 inhibitors like cemiplimab. That is based on the New England Journal data showing in the metastatic disease cohort of patients, response was seen in 28 out of 59 patients. That is a near 50% response. In that setting, in those responding patients, the duration of response exceeded 6 months in near 60%, and patients continue to have a response and receive cemiplimab without significant toxicity. Adverse events were manageable—diarrhea, fatigue, nausea and rash. And in these patients we have seen the ability to not only have response and durable response but to avoid morbidity. The response rate and duration are greater than we have seen with chemotherapy and EGFR inhibitors.

I would add that the multidisciplinary management in centers like ours and yours also centers on a discussion about next-generation sequencing and evaluation of other targets that appear in cutaneous squamous cell carcinoma and an evaluation for toxicity that is jointly managed with nursing, dermatology, and other people who are part of the team.

Dr. Schmults:
Thank you. I don't believe neoadjuvant therapy was part of the specific cemiplimab approval, but what kinds of scenarios could you see neoadjuvant therapy coming into play at this point in time?

Dr. Hamid:
Clearly, in patients who have had lesions that recur multiple times, they are an indication there, but also patients who have lesions where they are surgically resectable but surgery would cause severe morbidity, also patients where you want to preserve function and downstage the extent of resection. So these are where we discuss with patients a neoadjuvant approach using PD-1 inhibition.

Dr. Schmults:
For example, with our case 1, the patient with the large tumor abutting the joint space of the knee, that is a setting where the person is unresectable, but perhaps with neoadjuvant anti-PD-1, if the tumor could shrink enough that it comes away from that joint space, perhaps a surgical resection could be performed. So you can think of potential scenarios where an unresectable patient might be able to move into a resectable zone if the tumor can be shrunk with anti-PD-1 therapy.

Dr. Hamid:
Absolutely, completely agree.

Dr. Schmults:

Immune-related adverse events can occur when patients are treated with immune checkpoint inhibitors. Dr. Jambusaria, can you describe how you approach resolving these types of reactions?

Dr. Jambusaria:
Sure. So, immune-related adverse events occur in the setting of PD-1 inhibition because activation of T-cells can increase levels of pro-inflammatory cytokines and also increase levels of autoantibody formation. The most common side effects seen with PD-1 inhibition include fatigue, rash, and diarrhea, and these symptoms are generally mild and well-tolerated. However, it is possible to have more severe reactions. And when you have involvement of the cardiac system, endocrine, as well as neurotoxicity, the drug should be stopped even for minor reactions. In particular, I'd like to mention the endocrine side effects, which can be irreversible. It happens in approximately 10% of patients who get therapy, and usually, these reactions are irreversible. And even after stopping PD-1 inhibition, these patients may need hormone replacement therapy. The 2 most common types of endocrine reactions that occur can be hypothyroidism as well as diabetes from attacking the thyroid and pancreas respectively, and so these patients would need Synthroid or insulin replacement long-term.

The management of grade 1 and 2 toxicities is generally supportive with potential temporary discontinuation of treatment until the toxicities resolve and then restarting treatment. If you have a grade 3 or 4 toxicity, these patients will need cessation of therapy as well as initiation of prednisone, and if that is not helpful, infliximab infusions.

If you want to learn more about the management of immune-related adverse events on PD-1 inhibition, I would refer you to the American Society of Clinical Oncology's Clinical Practice Guideline which was published in the Journal of Clinical Oncology in June 2018.

Dr. Schmults:
Thank you very much. Thank you for participating in this CME activity. Please don't forget to take the posttest and complete the evaluation to receive CME credit.

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