CARCINOMAS & KERATOSES

Clinical insights into the world's most common skin cancers
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Cemiplimab for Treatment of Advanced Cutaneous Squamous Cell Carcinoma: A Game Changer

In This Issue

One of the reasons The Skin Cancer Foundation created Carcinomas & Keratoses is that the nonmelanoma skin cancers have a public perception problem. A Harris poll conducted earlier this year found that 42 percent of Americans have never heard of cutaneous squamous cell carcinoma (cSCC). In contrast, only 11 percent of Americans say they have never heard of melanoma. Furthermore, 72 percent of Americans don't understand that nonmelanoma skin cancers such as cSCC can spread and become life-threatening, while approximately 15,000 people in the U.S. with cSCC die of the disease each year. We want to help change that.

Michael R. Migden, MD, has been a leader in this charge. He is a professor in the Department of Dermatology at the University of Texas MD Anderson Cancer Center in Houston. Dr. Migden was principal investigator of the trial that led, in September 2018, to FDA approval of cemiplimab-rwlc (Libtayo), the first immunotherapy treatment for patients with advanced cSCC. Dr. Migden talked with Julie Bain, The Skin Cancer Foundation's senior director of science & education, to shed light on how this new treatment is improving outcomes for patients who previously had little hope — and is leading to exciting new research.

Photo: The University of Texas MD Anderson Cancer Center

The Feature

A New Era for Treatment of Advanced cSCC

Julie Bain: To what extent do you think cutaneous squamous cell carcinoma (cSCC) has been dismissed as one of the "less serious" skin cancers?

Michael R. Migden, MD: I think it depends on the perspective. If you're talking about the lay public or primary care physicians, they tend to worry more about melanoma. But among general dermatologists and surgical dermatologists, I wouldn't say cSCC is less of a concern. It's more of a concern than basal cell carcinoma (BCC), and widely known to have life-threatening potential.

It is important to distinguish between the more commonly encountered, surgically appropriate tumors and advanced cSCC tumors having limited treatment options. Factors that can put patients on the path to locally advanced and metastatic disease include: Some cSCC tumors inherently behave more aggressively. Treatment failure, such as excision that wasn't complete, or neglect, can also lead to increased tumor aggressiveness.

JB: It seems shocking that a patient could ignore a big, nonhealing lesion without understanding how serious it could be.

MRM: There is a spectrum of patient attitudes. Some are worried about every tiny spot, and on examination of their skin, many of the spots are barely visible. Other patients may have a large lesion that has been there for a long time, and they really aren't concerned about it.

JB: What was it was like to see patients who had advanced cSCC before cemiplimab was a treatment option?

MRM: We lost many of those patients. I lost a patient I had been seeing for multiple smaller tumors, when one of them became more aggressive and spread to locoregional lymph nodes. There are more patients who have died from locally advanced disease or locoregional metastasis than from distant metastasis. The general public may consider distant metastasis as the worst form, but that's not borne out by statistics. Patients with large, locally invasive lesions or with local lymph node involvement are at the highest risk for mortality.

JB: What would you do for those patients?

MRM: Prior to cemiplimab immunotherapy, there was no FDA-approved therapy for this diagnosis. Oncologists would typically use chemotherapy such as platinum agents or epidermal growth factor receptor (EGFR) targeted therapy for these patients. The drawback with both of those are significant tolerability issues. The public is aware that chemotherapy has substantial side effects. The EGFR targeted agents can also produce significant side effects. The most difficult problem was the lack of durability of any kind of response. If there was a response, it tended to be short-lived. Prior to immunotherapy, there was mortality within one to two years in a significant percentage of patients.

JB: Did you see a lot of those patients? That must have been a very discouraging time.

MRM: I would see patients who were taking chemotherapy or EGFR agents and who still had new skin lesions becoming a problem. Most patients on systemic therapy were managed with a multidisciplinary team, including oncology and head and neck surgery.

JB: What led you to this research?

MRM: I was active in studying hedgehog inhibitors for advanced BCC. During the time I was treating advanced BCCs, I was seeing these patients with advanced cSCC and thinking, *Why don't we have something that can help them? Why aren't we doing trials?* And I was also seeing success with anti-PD-1 agents in other cancers, including head and neck SCC (which is a very different disease from cSCC). I said, "Why aren't we using anti-PD-1 for this disease?"

Contacting multiple pharma companies asking for a cSCC trial, I was told, "Not that disease." "Not right now." "We're busy with lung and other types of cancer."

Regeneron, based on prior research, reached out to me, asking if I was interested. This led to my lead participation role in the EMPOWER study for cemiplimab.

JB: Why were you convinced that cSCC would react to anti-PD-1 checkpoint blockade therapy in a similar way to other cancers, like melanoma?

MRM: Melanoma has a higher tumor mutational burden compared to many other cancers, but it's still substantially lower than cSCC. We know from other cancers that higher mutational burden seems to be associated with better response to immunotherapy. This may be due to an association with greater neoantigen formation, so there are more targets for the immune system to respond to. And cSCC has the highest tumor mutational burden of any cancer in the cancer genome atlas.

JB: What do you know so far about the efficacy of cemiplimab?

MRM: We're showing objective response rates between about 44 and 50 percent — the range depending on which data cut and which cohort, whether it's local, advanced or metastatic. Interestingly and importantly, though, for locally advanced disease, which is a good percentage of the total, we're seeing a disease control rate of almost 80 percent.

Why is that important? Because when you're talking about advanced cSCC, you're talking about a disease that otherwise kills a substantial percentage of patients. It is remarkable that 45 to 50 percent of people respond, but disease control is perhaps more important than response. Disease control means complete response, partial response or stable disease. In effect, you're preventing people from progressing. You're "holding" them. If you can hold almost 80 percent of people from progressing on a path that typically leads to death, that's a big deal.

JB: What did you see in your own patients?

MRM: My personal experience with 17 patients was the majority having a durable response after therapy for one to two years. This depended on whether they had a complete response at one year and were able to go into observation or whether they continued on the therapy for the full course. Most of those patients who had a complete response remained with no evidence of disease even off therapy for more than a year. These are patients who previously would have been untreatable, where we would have said, "We have nothing that is likely to cure you." Now I see patients like that who are almost two years off of therapy with no evidence of disease. It is amazing.

JB: I think anyone reading this would want to know what that feels like.

MRM: It's very rewarding. Conducting clinical trials is a lot of work. There's a lot of routine data collection and review, and it can become quite tedious. When you see patients, you see the fear in their faces because they've been told, "We really don't have anything for you. You're not going to make it." When you see them go through this process where their tumor is

decomposing, even falling off, and the area is healing, and then being told at some point, "Hey, we can't find any evidence of your tumor," that makes it all worthwhile.

JB: It gives me goosebumps to hear that. Did you get to know some of these people pretty well?

MRM: Yes. I remember one gentleman who came in with his head lying on his right shoulder, and he could not straighten his neck at all because of the tumor. He had exposed bone that was being consumed by his cSCC. Not only was he told that he had an incurable cancer, but he was in a lot of pain, unable to conduct himself in any way resembling a normal interaction. And I've seen him recently, completely upright, with no evidence of disease.

The reconstructive surgeons who do free flaps felt comfortable that they could clean up the bone and put a large covering of tissue over all that area of previously chronic wound. Interestingly, they took bone and tissue throughout that wound site and processed it, looking for any residual tumor, and there was none found. So now the patient is back to his normal self, worrying about the normal daily life issues rather than about dying.

JB: Amazing. Will you continue to follow these patients?

MRM: Yes, we continue to follow them. The study protocol had a follow-up period built in, and then I continue to see the people who have completed that. I want to observe these patients as long as I can, observing what the durability is, not just during the study interval and the study follow-up, but over a much longer period of time.

JB: Is it true that with this drug the patients who have the strongest reaction or side effects often achieve the best response?

MRM: The answer is yes. Two things can happen. People can have immune-related adverse events. People can also have pseudoprogression, where you put someone on treatment, the site rapidly becomes inflamed and their target lesion looks like it's getting worse before it gets better. Both of those situations need to be quickly addressed and taken seriously, but either can also be associated with a better response. I think of it as increased sensitivity to therapy.

Some immune-related adverse events can be life-threatening, so no one should get this medication without thorough and thoughtful discussion of the potential risks versus benefits. That said, it's more common for people to have the lower grade immune-related adverse events, such as skin rash or hypothyroidism, for example. I tell all of my immunotherapy patients that the slightest new sign or symptom — a new headache, a new cough, new diarrhea — has to be evaluated thoroughly. You can't take anything for granted if you're on immunotherapy. You have to make sure that it's not going to become an acute, life-threatening event.

JB: How difficult is it to figure out how to address each one of those cases and determine the next step?

MRM: The best care, in my opinion, is multidisciplinary care. And I'm just one person in a multidisciplinary team. If I'm the primary in terms of writing the order, the responsibility for the study patient lies firmly with me. But if there is the slightest new finding that looks unusual, I look at it, I talk to the collaborator in internal medicine or medical oncology and we discuss them

in detail. Multidisciplinary care includes bringing in the appropriate specialists based on what is needed. If it's pneumonitis, for example, I would want a pulmonologist. Whether it's an immune-related adverse event or pseudoprogression, we want everyone on the team to be aware and chime in about their impressions.

JB: Is it important to get yourself to a cancer center or a bigger city that has this kind of multidisciplinary care available if you have advanced cSCC?

MRM: A cancer center that has an established multidisciplinary team is an advantage to the patient; it may be easier if you have formalized multidisciplinary care at a major academic center. That does *not* mean, though, that you can't achieve a multidisciplinary decision-making process in private practice, because you can. I know people in private practice who say, "I have my people. I have my internal medicine go-to person. I have my oncology go-to person. I have my head and neck surgeon go-to person." They may get on a conference call and share photos and so on.

JB: Can patients with autoimmune conditions and advanced cSCC benefit from cemiplimab?

MRM: Immunosuppressed patients or those with autoimmune disease were not included in the EMPOWER study because we needed to see how the disease would respond with a normal, intact immune system. If there's any dysregulation of the immune system, there's always concern whether immunotherapy will be effective or not, and what kind of impact it will have on the overall safety and health of the patient.

With that said, we know chronic lymphocytic leukemia (CLL), for example, can dysregulate the immune response, but that doesn't mean a CLL patient who has generally quiescent CLL can't be treated with this. That's a case-by-case decision that the prescriber would have to make. With kidney transplant patients, when they're on immunosuppression, you run a risk of turning on the immune system to where the patient's kidney will be attacked and lost by the process. But if a patient has serious, life-threatening cSCC and they have the option of dialysis, most patients would say they'd rather be alive, even if they have to go on dialysis and lose their kidney transplant. So it's case by case, and more studies are needed to better characterize how people with baseline immune dysregulation do on immunotherapy.

JB: Since this drug was approved about a year ago, how is it changing the landscape for cSCC?

MRM: Well, it's game-changing in that we have an approved therapy that — barring immune-related adverse events — has extremely good tolerability. Remember the prior treatments, both the chemotherapies and the EGFR targeted agents, come with a plethora of tolerability issues. I've had multiple patients tell me when they start immunotherapy that they actually feel better than they did before they started. They're not coming in complaining about this side effect and that side effect on a daily basis.

JB: What does the patient experience while getting the infusion?

MRM: You're getting an IV line connected into the vein, and a fluid is passing with the anti-PD-1 cemiplimab antibody. You're sitting or lying back in a chair, and the IV takes about 30 minutes to administer. Once it's done, they watch you to make sure you don't have any kind of reaction,

and then you're up and out of the chair. You get a bandage on the area, and you're back in three weeks for your next infusion.

We hope over time that, perhaps, there can be other routes of administration. And that's an active area of research and interest of mine, whether it's something that can be administered in an office that doesn't have IV facilities or at home. But it's early, and these are not currently approved routes of administration.

JB: Is there any role for radiation in treatment of advanced cSCC?

MRM: There is an adjuvant study for people who have undergone surgery and radiation to add post-treatment cemiplimab to investigate the potential to increase survival from otherwise very aggressive disease. They would typically get surgery and radiation and then their physicians would decide whether there's some other treatment that could hold them. There are plans for a neoadjuvant study as well.

JB: Have you seen any preliminary results from research on neoadjuvant therapy?

MRM: I'm a collaborator on an investigator-initiated trial here at MD Anderson led by Neil Gross, MD. It looks at neoadjuvant use where the patients get two preoperative doses IV and then undergo resection, which could include a composite resection, including bone, et cetera. And then postoperative radiation as indicated for their target lesions.

Editor's note: Those early results were presented in a poster presentation at the European Society of Medical Oncology and showed that one third of the 20 patients achieved a complete response on imaging. Slightly more than half had a pathologic complete response and no evidence of disease at the time of surgery. An additional three patients had significant pathologic response, suggesting that their disease might also have cleared with further treatment. The very good responses in this single site investigator-initiated trial suggest it should have a much larger follow-up multicenter international study.

JB: What else do you hope to accomplish down the road?

MRM: Combining cemiplimab with other agents is an active area of investigation, to look for efficacy in patients who don't respond to single agent immunotherapy. We're also looking at combinations to see if we can boost the response rate above 50 percent. Some of these are in clinical trials.

One niche that I'm very focused on is local delivery. I am the leader of a clinical trial for this, and I'm hopeful that we can get the treatment in the location where the cancer is and minimize normal tissue exposure. There is also a study combining IV cemiplimab with an oncolytic modified herpes virus that's injected directly into the tumor and revs the engine of the immune system to generate a local immune response.

If we can rev the immune response engine with an oncolytic virus and take the brakes off with an anti-PD-1 such as cemiplimab working at the same time, we might be able to do an even better job attacking these cancers.

Editor's View

Désirée Ratner, MD
Editor-in-Chief, *Carcinomas & Keratoses*

One Patient Dying of Cutaneous Squamous Cell Carcinoma Is Too Many

About 20 years ago, I was sitting in a conference when the moderator asked, "How many of you have ever seen a cutaneous squamous cell carcinoma (cSCC) metastasize?" Out of 40 or 50 people in the audience, I was the only one raising my hand. The moderator continued, "The reason that none of you are seeing cSCCs metastasize is that we're so good at managing these tumors. The number of metastases is lower than ever." I was stunned. One of my patients had just died of metastatic cSCC. I raised my hand again, but the moderator moved on. I wanted to say that once you've had one patient die of metastatic cSCC, all you want is to make sure that it never happens again. I didn't get the chance to say it, but that thought has stayed with me ever since.

The moderator of that long-ago conference wasn't the only one thinking that metastatic cSCC wasn't a significant problem. For years, the "second most common skin cancer" was underestimated by physicians and the public, partly because it was lumped together with basal cell carcinoma (BCC), which seemed logical because both were nonmelanoma skin cancers. BCC was a recognized public health issue because it was so common, but melanoma, "the deadliest skin cancer," was the only one thought to be dangerous. However, with the incidence of melanoma and nonmelanoma skin cancer rapidly increasing, more people than ever now appreciate the seriousness of a cSCC diagnosis.

Dermatologists stratify cSCC into those at low risk or high risk for metastasis. Tumors in high risk locations, and aggressive, large or recurrent lesions, are effectively managed with Mohs surgery or wide excision, with postoperative radiation sometimes recommended to decrease recurrence risk. Nevertheless, some patients still develop aggressive cSCC, and until recently there really wasn't anything to offer them. A diagnosis of metastatic disease was essentially a death sentence, with the majority of patients succumbing within one to two years despite aggressive chemotherapy.

Over the past few years, advances in immunotherapy have changed the lives of patients with aggressive cSCC. Cemiplimab-rwlc (Libtayo) was FDA approved in September 2018 for patients with locally advanced disease who are not candidates for treatment with surgery or radiation and for patients with metastases. Its approval was based on clinical trials showing a 47.2 percent overall response rate (43.5 percent partial response and 3.7 percent complete response rate) in a cohort of 59 patients, a median response time of approximately two months and over 60 percent durability of response. Furthermore, this drug was well tolerated with few treatment-limiting side effects. Results like these were practically unheard of — until now.

This third issue of *C&K* features an interview with Dr. Michael Migden, the lead investigator on the study that led to cemiplimab's approval. He discusses how he became involved in this

research, his experiences with advanced cSCC patients before and after the advent of cemiplimab, and how he and his colleagues are trying to increase response rates by using new technologies and drug combinations to enhance results. These innovations are extending the life spans, and improving the quality of life, of patients who would almost certainly have died just a few years ago. While we are lucky to be living in a time of advances like these, we as physicians now have an even greater responsibility — keeping abreast of new developments. By sharing them, we can help patients with advanced disease survive challenges that would previously have been insurmountable, while crossing our fingers that they will continue to thrive in the face of them.

Takeaway for Your Patients

- Each year, more than 1 million people in the U.S. develop cutaneous squamous cell carcinoma (cSCC), the second most common type of skin cancer. While it is less common than basal cell carcinoma (BCC), cSCC has a higher risk of becoming locally advanced or metastatic.
- Studies have shown that about 1.5 percent of patients with cSCC die of the disease — approximately 15,000 people in the U.S. each year.
- Cemiplimab is a type of immunotherapy called checkpoint blockade therapy, which harnesses the power of the patient's immune system to fight cancer.
- This drug was approved by the FDA in September 2018 for patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for treatment with surgery or radiation and for patients with metastases. The medication is given as an intravenous infusion every three weeks.
- While cemiplimab is a game changer, more research is underway to see if combining the drug with other agents may lead to efficacy in patients who don't respond to single agent immunotherapy.

Additional Resources

See SkinCancer.org for more information on treatments for advanced cSCC: https://www.skincancer.org/skin-cancer-information/squamous-cell-carcinoma/advanced-scc/

Learn more about the survey conducted by The Harris Poll on behalf of The Skin Cancer Foundation and in coordination with Regeneron and Sanofi about the lack of public awareness of cSCC: https://www.skincancer.org/blog/have-you-heard-of-cutaneous-squamous-cell-carcinoma/

Read more, including Dr. Migden's nuanced definitions of locally advanced and metastatic cSCC in this article: https://www.targetedonc.com/news/migden-reviews-updated-data-for-pd1-agents-in-case-review-of-cscc

Neil D. Gross, MD, professor of head and neck surgery at The University of Texas MD Anderson Cancer Center, discusses the phase II study of neoadjuvant cemiplimab-rwlc (Libtayo) prior to surgery in patients with stage III/IV cutaneous squamous cell carcinoma (cSCC) of the head and neck: https://www.onclive.com/onclive-tv/dr-gross-on-neoadjuvant-cemiplimab-in-head-and-neck-cscc

A phase 1 trial of a non-anti-PD-1 immunotherapy (called anti-LAG-3) combined with cemiplimab: https://investor.regeneron.com/static-files/eb82c1c0-b9c9-48ad-87c8-ef92f1947faa