Dealing With Non-Responders to Systemic Therapy for Basal Cell Carcinoma
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David E. Miller, MD, interviewed by Harrison P. Nguyen, MBA, MPH

TODD E. SCHLESINGER, MD, FAAD: Hello and welcome to *Dialogues in Dermatology*. I am Dr. Todd Schlesinger, your Editor-in-Chief. We have another exciting podcast for you today. We hope that you enjoy.—

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HARRISON P. NGUYEN, MBA, MPH: Hello. Welcome to an episode of *Dialogues in Dermatology*. My name is Harrison Nguyen and I'm a dermatology resident from the Emory University School of Medicine. Today, I am joined by Dr. David Miller to discuss a topic, "Dealing With Non-Responders to Systemic Therapy for Basal Cell Carcinoma." Dr. Miller is truly a unicorn, as he's one of the few clinicians in the country who is board certified in internal medicine, dermatology, and medical oncology. He currently practices at the Massachusetts General Hospital Cancer Center and at the Massachusetts Eye & Ear Infirmary, where he co-directs multidisciplinary clinics in advanced skin cancer. Welcome to *Dialogues in Dermatology*, Dr. Miller.

DAVID E. MILLER, MD: Thank you for that kind introduction, Dr. Nguyen. It's a real pleasure to be here. I've learned a lot from *Dialogues in Dermatology* over the years and it's a privilege to be able to contribute to this truly fabulous program.

HARRISON P. NGUYEN, MBA, MPH: Let's go ahead and dive into this topic, Dr. Miller. We know that basal cell carcinoma is the most common human malignancy, with some 2 to 3 million cases diagnosed per year. And while the majority are cured with approaches used by

dermatologists and dermatologic surgeons, I know that in your practice you often see patients that require multimodal care. Can you tell us a bit about the type of basal cell carcinoma patients you see in your practice?

DAVID E. MILLER, MD: That's correct, Harrison. Although the majority of basal cell carcinomas can be cured via excision or managed successfully with topical therapies, our practice focuses on patients with advanced basal cell carcinomas that are either 1) at very high risk of recurrence if treated by surgery, 2) curable by a surgery that will result in a significant reduction in the quality of life of that patient due to the functional or cosmetic consequences, or 3) are incurable by surgery or radiation.

HARRISON P. NGUYEN, MBA, MPH: And patients with advanced nonmelanoma skin cancer, like those that you just described, often benefit from multimodal approaches in care. Can you tell us about your team's approach at Mass Gen to the care of patients with advanced basal cell?

DAVID E. MILLER, MD: Given that these patients often require consideration of multimodal care, we regularly convene multidisciplinary teams, consisting of dermatology, surgical oncology, ENT, radiation oncology, radiology, and medical oncology to thoughtfully weigh the risks and benefits of the treatment options. Once we decide and then execute a plan, we rely not only on a multidisciplinary team, but also very much on an interprofessional team.—

--I work extremely closely with our advanced practice providers, who are instrumental in the delivery of care of the advanced BCC patient. Furthermore, optimal care requires a team of not only dermato-oncologists and advanced practice providers but also on practice nurses, social workers, physical therapists, occupational therapists, nutritionists, palliative care specialists, and administrative assistants. It is truly a team effort.

HARRISON P. NGUYEN, MBA, MPH: It truly does sound like a team effort. And thank you so much for painting us a picture of your patient population and that team-based approach to the management of the advanced BCC patient. So while the advanced patient may benefit from surgical and radiation, as a dermato-oncologist, I know you think a lot about systemic treatments. Can you begin to tell us about how you approach systemic therapy for the advanced BCC patient?

DAVID E. MILLER, MD: Fortunately for patients with advanced disease, we have several systemic options that can deliver clinical benefit. These options are the direct result of our improved understanding of the molecular pathogenesis of this disease, both from a cancer cell-intrinsic as well as a cancer cell-extrinsic perspective. And when I talk about cancer cell intrinsic mechanisms, I'm referring to intracellular circuits, such as the Hedgehog pathway.—

--And when I speak of cancer cell extrinsic mechanisms, I'm referring to intercellular interactions in the tumor microenvironment, such as those between neoplastic and immune cells. So let's begin by discussing cell intrinsic mechanisms in this disease, given that understanding of key players and Hedgehog pathway led to the first FDA approvals of systemic therapy in advanced BCC. Now, this pathway has been known about for decades and transmits information to embryonic cells required for proper cell differentiation.—

--Sonic Hedgehog, which was discovered and named in the mid-'90s, is the best studied ligand of this pathway in humans. Sonic is secreted by cells and when it reaches its target cell, it binds to the patched-1 receptor. In the absence of ligand, patched-1 inhibits smoothened and downstream protein in the pathway. The binding of Sonic Hedgehog to patched-1 releases smoothened inhibition and leads to activation of the glioma-associated oncogene transcription factors GLI1 and GLI2, likely via its interaction with an intermediary protein, SUFU, or suppressor of fused that acts as an inhibitor of GLI1 and GLI2.—

--To underscore the importance of the molecular components I just described, it is thought that upwards of 70 to 90 percent of sporadic BCCs have mutations in patched-1, perhaps another 20 percent have mutations in smoothened, and between 5 and 10 percent have mutations in SUFU.

HARRISON P. NGUYEN, MBA, MPH: Wow, 70 to 90 percent of sporadic BCCs with mutations of patch-1. Thank you for that overview of an intricate but an important pathway. And this pathway it seems has produced FDA approved therapies for patients with advanced disease and is helping us understand potential strategies for additional approaches to help patients when these therapies fail to produce a clinical benefit. Can you now walk us through your approach to therapy in the first line setting?

DAVID E. MILLER, MD: My approach to patients in need of systemic therapy is to begin treatment with a monotherapy approach, with an FDA approved smoothened inhibitor if a clinical trial is not available. As the listeners of this program already know, there are two FDA approved smoothened inhibitors for advanced BCC: vismodegib and sonidegib. Vismodegib was approved in 2012 based on the strength of the data from the ERIVANCE trial in which 33 patients with metastatic disease and 63 patients with locally advanced disease were treated with 150 mg by mouth once daily dosing.—

--Objective response rates of 30 percent in the metastatic and 43 percent in the locally advanced setting were seen, with a median duration of response of 7.6 months. Subsequently in 2015, 66 patients with locally advanced disease were treated with the smoothened inhibitor sonidegib. Approval was based on a response rate of 56 percent and a median duration of response of 26.1 months. Both of these medications are important drugs and play a critical role in patients with advanced disease. Indeed in the real world setting, disease control rates have been reported to be as high as 80 to 90 percent.

HARRISON P. NGUYEN, MBA, MPH: Disease control rates as high as 80 to 90 percent, that's wonderful. Now, of course, it's not as perfect as we would like or else we wouldn't be having this topic of discussion. And so to that point, you've talked about the benefits of vismodegib and sonidegib. Can you tell us about some of the challenges you faced when using these agents?

DAVID E. MILLER, MD: The benefits of smoothened inhibitors include clinically meaningful reductions in tumor size. The two major challenges include the fact that nearly all patients experienced significant toxicity. And most patients will become either intolerant to those adverse effects and/or the tumors develop resistance. Indeed, one of the key arts of oncology is managing the side effects of antineoplastic therapies. With Hedgehog pathway inhibitors, there are several very important side effects to discuss.—

--To begin, let's just start with the boxed warning. The boxed warning is directly related to how the parent compound of vismodegib and sonidegib were discovered. That dates back to the 1950s amazingly, when Idaho sheep ranchers couldn't figure out why a batch of their lambs were being born with unusual birth defects. The animals had underdeveloped brains and a single eye planted cyclops-like in the middle of their foreheads.—

--In 1957, they called in scientists from the U.S. Department of Agriculture to investigate. The scientists worked for over a decade to solve the mystery. One of them, Lynn James, lived with the sheep for three summers before discovering the culprit, corn lilies. When the animals moved to higher ground during droughts, they snacked on the flowers. The lilies, it turned out, contained a poison, later dubbed cyclopamine, that stunted developing lamb embryos.—

--Cyclopamine was then further refined to produce vismodegib and sonidegib. Therefore, patients must be thoroughly counseled as to potential risks to developing fetuses. Now, while embryo fetal toxicity is the most important side effect to be aware of, fortunately it is avoidable

with counsel. Unfortunately, what seems to be inevitable for most patients is alterations in taste, muscle cramps, and alopecia.—

--And while mitigation strategies do exist, these side effects often accumulate in time and necessitate treatment holidays for the vast majority of patients.

HARRISON P. NGUYEN, MBA, MPH: Dr. Miller, I love that story about Lynn James and living with the sheep. That's science at its best, so thank you so much for sharing that. Dr. Miller, you mentioned that the majority of patients either become intolerant and/or progress on first line therapy. What second line systemic therapy options exist for advanced basal cell carcinoma?

DAVID E. MILLER, MD: Fortunately, insights into the role of the immune system in the tumor microenvironment has led to an important second line therapy that was approved by the FDA in February 2021, cemiplimab-rwlc. Cemiplimab, an anti-PD-1 antibody indicated for locally advanced metastatic cases previously treated with a smoothened inhibitor or for whom a smoothened inhibitor is not appropriate, was granted approval based on EMPOWER-BCC-1, a trial of 84 patients with locally advanced and 28 patients with metastatic disease.—

--Response rates were seen in 29 percent of patients with locally advanced and 21 percent with metastatic disease. Five patients in the locally advanced cohort had a complete response. Importantly, this study establishes the proof of concept of the role of immune checkpoint inhibitors in basal cell carcinoma. We knew that monoclonal antibodies against PD-1 and PDL-1 had activity in diseases like melanoma, merkel cell carcinoma, and squamous cell carcinoma. And now as a result of EMPOWER-BCC-1, we know this pathway is important in BCC.

HARRISON P. NGUYEN, MBA, MPH: So response rates of 29 percent of patients with locally advanced and 21 percent with metastatic disease. That seems to not be the majority, that seems to perhaps leave a good deal of patients who are not responding. Are there any

biomarkers at this time that can help us identify patients which are more likely to respond, Dr. Miller?

DAVID E. MILLER, MD: Unfortunately, we do not. The EMPOWER-BCC-1 investigators performed exploratory analyses on bio specimens taken during the trial and assessed them as to whether tumor mutation burden or loss of class I major histocompatibility complex could help distinguish responders from non-responders, but neither proved to be a reliable predictor.

HARRISON P. NGUYEN, MBA, MPH: So no biomarkers yet. But overall, it seems like we've still come a long way. We have two first line options and one in the second line setting. Can you now tell us about your approach to dealing with non-responders to systemic therapy for basal cell carcinoma?

DAVID E. MILLER, MD: Resistance to available strategies poses a significant therapeutic dilemma for our patients. We've learned that resistance to Hedgehog pathway inhibitors may develop via disruption of the drug binding site through smoothened mutations. Indeed, most patients with Hedgehog pathway inhibitor resistance have mutations in smoothened, regardless of whether the resistance is primary or secondary. One approach to addressing this resistance is to switch agents after intrinsic or acquired resistance is appreciated.—

--Overall though, this is a data low zone, with case reports describing clinical experience. A *JAAD* case report in 2017 described intracranial regression of an advanced BCC using sonidegib and itraconazole after failure with vismodegib. Indeed, itraconazole, the triazole antifungal we know well, binds to smoothened at a site distinct from the other smoothened inhibitors. And it's been investigated in combination with arsenic trioxide for patients with front line smoothened inhibitor resistance.—

--Arsenic trioxide, which destabilizes GLI2 to inhibit transcription of target genes of the Hedgehog signaling pathway in combination with itraconazole, was studied in a small clinical trial of five patients with metastatic disease who experienced progression on a front line smoothened inhibitor. Of the five patients, three completed three cycles of treatment and two discontinued treatment, owing to disease progression or adverse events.-

--Overall, arsenic trioxide and itraconazole reduced GLI1 messenger RNA levels by 75 percent from baseline, which was the primary endpoint of the study. The best overall response after three treatment cycles was stable disease in three patients. Importantly, none had tumor shrinkage. So my enthusiasm to use this combination overall has been tempered.

HARRISON P. NGUYEN, MBA, MPH: So we do have itraconazole and arsenic trioxide in the armamentarium but really none had tumor shrinkage. So perhaps this isn't quite the solution long term for us. Are there any other potential targets that have been investigated in a study of smoothened inhibitor resistance?

DAVID E. MILLER, MD: Yes, because the phosphatidylinositol 3-kinase pathway has been implicated in smoothened inhibitor resistance. The efficacy and safety of combining smoothened inhibition with PI3 kinase inhibition has been examined. An exploratory, open-label, investigator-initiated study of ten patients was conducted to evaluate the efficacy and safety of combination sonidegib with the pan-PI3K inhibitor, buparlisib, in advanced BCC.—

--Unfortunately, this study was terminated early, after a total of 8 grade III adverse events in 50 percent of the patients. Seven of the patients were evaluated for efficacy, five with previous smoothened inhibitor failure. This combination achieved an overall response rate of 14.3 percent and a disease control rate of 71 percent. One patient had a partial response and four patients remained with stable disease.

HARRISON P. NGUYEN, MBA, MPH: In addition to combination therapies with targeted therapies, what approaches are being looked at to capitalize on our knowledge of the immunologic mechanism in the tumor microenvironment?

DAVID E. MILLER, MD: Building off our experience in diseases like melanoma, where combining PD-1-directed therapies with additional immune checkpoint inhibitors, like CTLA-4 and LAG-3, which have yielded improved response rates in melanoma, investigators at Johns Hopkins are conducting an open label phase 2 signal seeking study of the anti-PD-1 antibody, nivolumab, plus the LAG-3 inhibitor relatlimab, or the CTLA-4 inhibitor ipilimumab, for patients with advanced BCC.—

--I'm eagerly awaiting the results of that study, as it should provide us with important insights in the utility of combining immune checkpoint blockade in advanced BCC.

HARRISON P. NGUYEN, MBA, MPH: Thanks for giving us insight into that novel kind of current study. And we'll have to stay tuned for the results of that. That really underscores the point of continued clinical investigation and how important it is to find novel therapeutics with activity in this disease. Are there additional strategies that you've tried with existing armamentarium?

DAVID E. MILLER, MD: Another strategy is to reduce the likelihood of developing acquired resistance via utilization of smoothened inhibitors in a neoadjuvant setting. Hedgehog pathway inhibitors are being studied as neoadjuvant therapy to reduce lesion size, to enable the possibility of surgical excision in candidates previously unsuitable for surgery. With this strategy, the development of resistance may be less likely, as patients who respond to initial treatment will be able to have their tumors removed.—

--In an open label study investigating the use of vismodegib prior to surgery in patients with advanced disease, the investigators noted a mean decrease from baseline in target tumor surgical defect area of 27 percent in patients treated with at least three months of vismodegib. Among the eight patients who participated in a two year follow up, neoadjuvant treatment decreased the surgical area by 35 percent and allowed for tumor clearance with no recurrence at a mean follow up of nearly two years.—

--In another study, the VISORB trial, 34 patients with globe and lacrimal drainage system threatening basal cell carcinoma, were treated with vismodegib. A total of 56 percent of patients demonstrated complete tumor regression by physical examination and 47 percent had complete regression by cross-sectional imaging. Roughly 80 percent of the patients underwent surgery, of which nearly two-third had no histologic evidence of disease, 22 percent had residual disease with clear margins, and 11 percent had residual disease extending to the margins.—

--These results are also important because tumors like these present a challenge, as the labeled indication for frontline systemic therapy is for tumors that have recurred following surgery or in those who are not candidates for curative surgery or radiation. However, in clinical scenarios like these, the curative surgical approach, for example, complete removal of the eye and its associated structures, can lead to functional deficits that are worse than non-curative approaches.—

--Not surprisingly, patients have reported significant declines in their quality of life after having surgeries such as exenteration. In addition, for advanced periocular basal cell tumors, even surgical approaches which are successful in sparing the eye can be problematic because they can result in disfigurement and/or the permanent loss of function due to alterations in key associated structures.—

--Therefore, one of our key objectives when we develop a management plan for patients with periocular basal cell carcinomas is preservation of the eye and its function. Thus, results like those seen in the VISORB trial highlight the potential utility of neoadjuvant treatment for certain types of advanced basal cell carcinoma.

HARRISON P. NGUYEN, MBA, MPH: Dr. Miller, this has certainly been a very thought-provoking and interesting conversation. We've clearly made a lot of progress in this disease but obvious challenges remain for patients that progress on first and second line therapies. On behalf of *Dialogues* listeners, I'd like to thank you for your time today, Dr. Miller. I've learned a lot about how to manage non-responders to systemic therapy for basal cell and look forward to following your work in advancing management for these patients. Thanks again, Dr. Miller, and we hope to have you on again in the future with more updates for our listeners.

DAVID E. MILLER, MD: You're very welcome, it was my pleasure.

TODD E. SCHLESINGER, MD, FAAD: Thank you to Genentech, a member of the Roche Group, for supporting this episode of *Dialogues in Dermatology*.—

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