Management of Unresectable BCC
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Desiree Ratner, MD, FAAD, interviewed by Maral Kibarian Skelsey, MD, FAAD

MARAL KIBARIAN SKELSEY, MD, FAAD: Welcome to this episode of *Dialogues in Dermatology*. I'm your host, Maral Kibarian Skelsey. I'm very happy to welcome today Dr. Desiree Ratner while we talk about Management of Unresectable Basal Cell Carcinoma. Dr. Ratner is a Clinical Professor of Dermatology at NYU's Grossman School of Medicine. She's Co-Editor of the *Dermatologic Surgery* journal, Associate Editor of the *Journal of the American Academy of Dermatology*, and a leader in the field of cutaneous oncology, as well as a practicing Mohs surgeon in New York City. We're very happy to have you here, Dr. Ratner, thank you for joining us.

DESIREE RATNER, MD, FAAD: I'm very happy to be here, thank you.

MARAL KIBARIAN SKELSEY, MD, FAAD: Unresectable basal cell carcinoma is a rare entity but it does occur. What's kind of a general number in terms of how many people are affected by this really devastating consequence?

DESIREE RATNER, MD, FAAD: As you said, it's difficult to come up with an exact number. If hypothetically there are 3.5 million people with this condition in the United States alone, you could say theoretically anywhere from 1 to 10 percent of the population has it, 10 percent seems a little bit high. But 1 percent of 3.5 million would be about 35,000 people a year.

MARAL KIBARIAN SKELSEY, MD, FAAD: And for these people, what's the general landscape of agents that are available for nonresectable or metastatic basal cell?

DESIREE RATNER, MD, FAAD: It used to be that really very little could be done, because surgery would be so difficult to perform with such morbidity and radiation often was unsuccessful. These are still options but we aren't as reliant on those as we used to be. We now

have the oral hedgehog inhibitors, which are a class of drugs that's really changed the management of these patients. For those patients who don't respond even to those, we have an additional second line agent, which is a targeted IV drug which has also been successful in cutaneous squamous cell carcinoma.

MARAL KIBARIAN SKELSEY, MD, FAAD: So the cemiplimab or the PD-1 inhibitor. First let's go back to the hedgehog inhibitors. How are those used for first locally aggressive versus metastatic basal cell carcinoma?

DESIREE RATNER, MD, FAAD: In locally aggressive basal cell carcinoma, they are traditionally used as a drug that's taken on an ongoing basis. There are two agents that are commonly used, vismodegib and sonidegib and they are taken once a day. They can be taken until either the onset of side effects or the onset of resistance. For a long time, that's all we really thought about.—

--Those agents can now be used in a neoadjuvant way as well, meaning that they can be taken for a shorter period of time, six to eight weeks or a little bit longer, just to shrink the footprint of the tumor so that surgery can then be performed, taking a lesion that was unresectable or very difficult and making it a much more easily resectable lesion.--

--The last option is for patients who can't tolerate the drugs at their daily doses because of the side effects, there are alternative regimens that can be used, such as drug holidays where patients are off the drug for a period of weeks. There are also options which are not formally approved but which I've used, basically tapering the drug to a very low level where it remains effective, with a minimum of side effects.

MARAL KIBARIAN SKELSEY, MD, FAAD: So you're able to taper the dose and still have efficacy. And that's about over a period of like six to eight weeks you're doing that?

DESIREE RATNER, MD, FAAD: When I use the drug neoadjuvantly, I keep people on a daily dose for six to eight weeks at conventional doses, get them to the point that I want them to be and then operate, and then they don't have to be on the drug anymore. For people who require long term oral hedgehog inhibitor treatment, who can't tolerate surgery for whatever reason but also can't tolerate the side effects, I put them on a program where I start them at conventional doses for a month or so, get an effect from the drug, and then taper them down to every other day, then every third day, then every fourth day, basically keeping patients on that regimen for a month or so, say every other day for a month, checking them, and then taking them down to every third day.—

--Basically, the goal is to get them to the lowest dosage where they're getting a therapeutic effect, while minimizing the side effects that they have. And I've found that I can get patients down to basically a pill a week and still retain efficacy of the medication. But this is after they've been on the drug at full dose for a while, so they've gotten the effect that they need.

MARAL KIBARIAN SKELSEY, MD, FAAD: And you're still seeing some side effects at these lower doses?

DESIREE RATNER, MD, FAAD: The side effects resolve, as far as I can tell. Patients have grown back their hair, they no longer have an issue with muscle cramps or dysgeusia.

MARAL KIBARIAN SKELSEY, MD, FAAD: What are the leading side effects that lead to discontinuation of the drug in your hands?

DESIREE RATNER, MD, FAAD: There are really three big ones. The first is hair loss or alopecia, which tends to happen within a couple of months after starting the drug it becomes noticeable. The second is muscle cramps, which can be very uncomfortable and somewhat debilitating, and that's probably one of the two greatest limiting side effects. The third is taste

disturbances or dysgeusia, where patients say that food doesn't taste like normal food anymore, it can be tasteless, it can have a strange taste, this sort of variable set of symptoms that go along with taste disturbances. But all of those are rate limiting factors in terms of patients continuing the drug.

MARAL KIBARIAN SKELSEY, MD, FAAD: What about resistance?

DESIREE RATNER, MD, FAAD: Resistance is less common, but occurs. There are two forms of resistance. There's primary resistance, where basically the drug doesn't work from the beginning, and that's pretty unusual. And then there's secondary resistance, where secondary resistance can happen in a couple of different ways. One is that the patient has been on the drug for a long time and has developed a secondary resistance, where the drug stops working after having worked for quite some time. That's really the most common thing that we see.

MARAL KIBARIAN SKELSEY, MD, FAAD: In addition to resistance, what about the association with increased risk of squamous cell carcinoma? Is that real? Have you seen it?

DESIREE RATNER, MD, FAAD: I do think it's real. I have not seen it, and it may be because I tend to keep my patients who need long term therapy on lower doses rather than the full dose, but I've never seen it, so I can't say.

MARAL KIBARIAN SKELSEY, MD, FAAD: So for metastatic basal cell carcinoma, there's really only one option?

DESIREE RATNER, MD, FAAD: There's only one hedgehog inhibitor that's an option, which is vismodegib.

MARAL KIBARIAN SKELSEY, MD, FAAD: And then for unresectable basal cell carcinoma, you have two options?

DESIREE RATNER, MD, FAAD: Correct. For locally advanced basal cell carcinoma, there are two oral options. There's vismodegib and sonidegib, which basically have equivalent rates of effectiveness in locally aggressive basal cell carcinoma.

MARAL KIBARIAN SKELSEY, MD, FAAD: So if a patient fails either of those two with advanced basal cell carcinoma, what's the next step?

DESIREE RATNER, MD, FAAD: Well, the next step, assuming that you don't want to start the other oral hedgehog inhibitor, is to use cemiplimab, which is a PD-1 inhibitor. And that is a second line drug. It's not something that we start immediately. And basically the way it works is by enhancing the patient's immune system and helping the T-cells to have the anti-tumor effect that they need to have.

MARAL KIBARIAN SKELSEY, MD, FAAD: Come back for a minute to the hedgehog inhibitors. How often do you switch from one agent to another if they're intolerant to the toxicities or they're unresponsive?

DESIREE RATNER, MD, FAAD: I don't switch from one to the other. I've only had one patient in whom that was done, and the other agent was not effective either. The side effects are the same, so I tend not to go from one to the other.

MARAL KIBARIAN SKELSEY, MD, FAAD: So with the PD-1 inhibitors, how quickly do you see a response?

DESIREE RATNER, MD, FAAD: So the first thing to say about cemiplimab is its response rates are a little bit lower. So for patients who are on oral hedgehog inhibitors, their response rates are about 50 percent. In locally advanced BCC, for patients with BCC's who do not respond and require cemiplimab, you've only got about a 32 percent rate of response, so it's lower to begin

with. The vast majority of those are partial responses and a few complete responses have been seen.—

--I can't answer how quickly it takes for them to respond but once patients do respond, they tend to have a durable response for quite some time, which is on the order of months to a year, not years and years, because this is still a new drug so we don't have long term follow up.

MARAL KIBARIAN SKELSEY, MD, FAAD: And is there a difference in their response rate for metastatic versus locally advanced?

DESIREE RATNER, MD, FAAD: The response rates for metastatic patients are a little bit lower. So there's about a 24 percent overall response rate to cemiplimab in the population of patients who doesn't respond to hedgehog inhibitors.

MARAL KIBARIAN SKELSEY, MD, FAAD: What are the main side effects for these patients?

DESIREE RATNER, MD, FAAD: The side effects of PD-1 inhibitors that are common are things that you think of traditionally with any kind of systemic agent for cancer. So it's fatigue, it's rash, it's diarrhea. But there's also a set of side effects that are less common that we have to worry about, which are immune-related side effects. So these include things like hepatitis, thyroiditis, basically any organ can develop an immune response.—

--So patients develop diabetes, they develop problems with their adrenal gland, their pituitary, these are all endocrinopathies, which are relatively uncommon but all of which have been reported with these agents.

MARAL KIBARIAN SKELSEY, MD, FAAD: What are the options and also with these immune side effects for patients who are recipients of solid organ transplants?

DESIREE RATNER, MD, FAAD: That's more of a problem because you worry about rejection in these patients with anything that alters the immune system. In patients who have renal transplants, because you have the option of going to dialysis if the graft doesn't make it, there's a greater willingness to use the medication in these patients. There's been one small study of renal transplant patients who received cemiplimab, who received high doses of prednisone or steroids and were also switched to the mTOR inhibitors.—

--And as it turned out, they did not reject their grafts and were able to tolerate cemiplimab, which is hopeful for patients who have organ transplants who develop these diseases, but this still isn't the mainstream treatment by any means.

MARAL KIBARIAN SKELSEY, MD, FAAD: How about for the bone marrow transplant patients, is there an increased risk of graft-versus-host?

DESIREE RATNER, MD, FAAD: I did read one study about the bone marrow transplant patients, and I can't remember all the details of it. But it's a population where this drug has to be used with caution.

MARAL KIBARIAN SKELSEY, MD, FAAD: Do you have any specific recollections of that study?

DESIREE RATNER, MD, FAAD: No, I don't. I just have some recollection that it's another category of patient that has difficulty with the PD-1 inhibitor. They're such powerful drugs and they have the ability to affect so many different organ systems that these patients really have to be monitored carefully.

MARAL KIBARIAN SKELSEY, MD, FAAD: What other contraindications are there for cemiplimab?

DESIREE RATNER, MD, FAAD: In patients with basal cell carcinoma?

MARAL KIBARIAN SKELSEY, MD, FAAD: Yes.

DESIREE RATNER, MD, FAAD: Well, it's really used only for patients who either aren't a suitable candidate for treatment with hedgehog inhibitors or who failed the agent. So it's really got a very narrow indication in patients with basal cell. Really, if the patient has had a transplant, there's got to be a multidisciplinary group involved to determine whether they are either a candidate for the drug or whether, with some sort of modified immunosuppressive regimen, it might be considered.

MARAL KIBARIAN SKELSEY, MD, FAAD: For the unfortunate patient who also fails cemiplimab, would they be candidates for chemotherapy? Or what other options do they have?

DESIREE RATNER, MD, FAAD: They would absolutely be candidates for chemotherapy. They're usually platinum-based regimens. They tend to have relatively low cure rates. Of course, they're always an option but once patients have failed both agents, chances are they're not going to do all that well.

MARAL KIBARIAN SKELSEY, MD, FAAD: Have you had any difficulty in terms of access to either the hedgehog inhibitors or cemiplimab for your patients?

DESIREE RATNER, MD, FAAD: Cemiplimab is something that I personally do not prescribe, so I send my patients to medical oncology for that. Somehow, they've always managed to obtain whatever drug is needed for these patients, so I don't really worry about that. In terms of the hedgehog inhibitors, I use primarily vismodegib. The company that makes vismodegib has a terrific patient access program that helps its patients to obtain insurance authorization for the drug if they're eligible. So most of the time, we've managed to get coverage for the drug for our patients. Occasionally, that has not been the case.

MARAL KIBARIAN SKELSEY, MD, FAAD: But for the most part, they're able to get access?

DESIREE RATNER, MD, FAAD: Yes.

MARAL KIBARIAN SKELSEY, MD, FAAD: What is the future for the patients who have either metastatic or locally advanced basal cell, what's coming down the pipeline?

DESIREE RATNER, MD, FAAD: There are newer classes of hedgehog inhibitors that are coming down the pipeline which affect other places within the hedgehog pathway. There are a number of steps along the pathway that can be effective and it's usually when patients develop resistance that one of those other pathways has come into play. So those agents are coming along. And then I would imagine that other PD-1 inhibitors, as they're developed and tested, will also become possibilities for these patients.

MARAL KIBARIAN SKELSEY, MD, FAAD: Dr. Ratner, how do patients with locally advanced basal cell carcinoma benefit from a multidisciplinary approach?

DESIREE RATNER, MD, FAAD: For these patients, it's essential that a team be in place to help with their management. The reason is that they may require imaging, they may require surgical specialists to weigh in, they certainly need medical oncology. Before a drug such as a PD-1 inhibitor is implemented, all approaches need to be looked at. So for these patients, a multidisciplinary team needs to be in place, with ready access to, in particular, medical oncology, as these are the specialists who will most likely take over their management. But if patients don't respond, then there needs to be a backup team in place.

MARAL KIBARIAN SKELSEY, MD, FAAD: And that might be difficult for patients who are in remote areas and don't have access to an academic center where there is a tumor board or multidisciplinary team. Do you have any suggestions for those scenarios?

DESIREE RATNER, MD, FAAD: That's true. The advantage of the hedgehog inhibitors is that they're oral drugs that we, as dermatologists or dermatologic surgeons, can easily prescribe and monitor these patients, which I do. In the event that they don't respond, then the key point person, if a team isn't available, would be a medical oncologist who is comfortable prescribing a PD-1 inhibitor. As long as you have those elements in place, there's still a way to treat these patients, it just wouldn't be in the setting of a larger team.

MARAL KIBARIAN SKELSEY, MD, FAAD: But having that relationship with oncology is critical for these patients?

DESIREE RATNER, MD, FAAD: Absolutely. And the ability to have quality imaging for these patients, as well, is important because that may be an important part of their monitoring if the extent of their disease isn't visible and can't be tracked by the dermatologist, for example.

MARAL KIBARIAN SKELSEY, MD, FAAD: Do you have a particular imaging regimen or routine for head and neck tumors?

DESIREE RATNER, MD, FAAD: I tend to refer those patients to others for that imaging because they're the ones who are going to be monitoring them. So if there's a concern about perineural involvement, they're going to be getting an MRI. If not, more often they're going to have a CT to look at soft tissues. But I'm not generally the one who selects that monitoring. I let those who are going to be doing the follow up order those and continue to order them.

MARAL KIBARIAN SKELSEY, MD, FAAD: What's the future for the topical hedgehog inhibitor?

DESIREE RATNER, MD, FAAD: That's interesting. I've had a few basal cell carcinoma patients, basal cell nevus patients, who were in the topical hedgehog studies and they were very successful in eliminating superficial basal cells on the face and also decreasing the size of

basal cells that were treated. So my patients who were on it were very, very happy with those agents. Unfortunately, the study has been stopped and I'm not sure when it's going to be resuming. But the topical hedgehog agents have huge promise in terms of treating particularly basal cell nevus patients.

MARAL KIBARIAN SKELSEY, MD, FAAD: Well, that's encouraging that we have some more in our armamentarium. Are there any final thoughts, Dr. Ratner?

DESIREE RATNER, MD, FAAD: I wouldn't have imagined 20 or 25 years ago that we would have the treatments that we do now. It used to be that a locally advanced basal cell carcinoma or metastatic basal cell carcinoma was essentially a death sentence. There wasn't really anything that we could do that was effective. And now we can give these patients a quality of life that I would never have dreamt of before. And we're now able to treat patients who before were completely written off.—

--So I would envision that as we become better and better at thinking outside the box and thinking about new possibilities for treating these patients, we'll have additional options come into play.

MARAL KIBARIAN SKELSEY, MD, FAAD: Well, that's encouraging, so thank you for that, and for being a real leader in this field, and for sharing your expertise and your time.

DESIREE RATNER, MD, FAAD: It's my pleasure, thank you for having me.

MARAL KIBARIAN SKELSEY, MD, FAAD: Thank you to our listeners.