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Managing MAPK Inhibitor Adverse Events in Pediatric Low-Grade Gliomas

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Day One Biopharmaceuticals. Here's your host, Dr. Alexandria May.

Dr. May:
This is *Project Oncology* on ReachMD, and I'm Dr. Alexandria May. Joining me to discuss how we can manage adverse events associated with MAPK inhibitors for pediatric low-grade gliomas are Ms. Bridget Archambault and Ms. Shannon Raber. Ms. Archambault is a certified pediatric nurse practitioner in neuro-oncology at Duke Children's Health Center and the Preston Robert Tisch Brain Tumor Center in Durham, North Carolina. Ms. Archambault, thanks for being here today.

Ms. Archambault:
Thank you for having me.

Dr. May:
And Ms. Raber is an acute care pediatric nurse practitioner at the UCSF Benioff Children's Hospitals in San Francisco, California. Ms. Raber, it's great to have you here with us as well.

Ms. Raber:
It's great to be here. Thank you.

Dr. May:
To begin, we know that keeping patients on MAPK inhibitor therapy can be challenging, especially early on in the treatment journey. Based on your experience, Ms. Archambault, what are the biggest drivers of treatment discontinuation?

Ms. Archambault:
Adverse effects can be a primary reason that patients or families choose to discontinue therapy. And I think it depends on the severity of it and whether it's impacting the patient's quality of life or poses a threat to their life expectancy.

When I think of the adverse effects, rash comes to mind as it's the most common with MAPK-targeted therapy. Many times, the rashes are manageable, but when a patient has a grade 4 rash that involves the majority of their body, it can be disfiguring and quite painful, so that can be a reason that families choose to discontinue therapy. Other things that can impact quality of life include fatigue, which is, again, generally manageable, but if it's impacting the patient's ability to participate in their activities of daily living, then that may be another reason.

And of course, there's always the rare but serious complications as well that can be a reason for discontinuing therapy, including impaired cardiac systolic function or significant ocular complications.

Dr. May:
And, Ms. Raber, I'd love to get your perspective on this as well. In your practice, do you see similar drivers of discontinuation? And what adverse events do you watch for depending on the mechanism involved, whether that's a type I BRAF inhibitor, a MEK inhibitor, or a type II RAF inhibitor?

Ms. Raber:
I think Ms. Archambault spoke to most of the things that we're experiencing as well in our patient population. I think another point is that depending on the type of medication, some of them have restrictions around eating around the time of medication administration, and for

children especially, that can be really challenging. So it's important to come up with plans with families on how it works best in their lives—to be successful in taking the medicine and getting their meals in.

For specific drugs and depending on the agent, we do watch for the cardiac toxicities with MEK inhibitors especially and the ocular toxicities that were touched on. Maybe a little more specific to the type II RAF inhibitors is monitoring linear growth in children and deciding on treatment regimens depending on times of growth. And, of course, always the skin toxicities that we were talking about.

Dr. May:
With that background in mind, let's talk about how we manage one of the most common adverse events we see in practice, just like you mentioned: cutaneous toxicities. Recent Delphi consensus recommendations emphasize a proactive approach, including early prophylactic skincare and stepwise management strategies for toxicities like eczematous rash, acneiform rash, and paronychia. So if we come back to you, Ms. Archambault, how do you use these recommendations to get ahead of cutaneous adverse events? And when do you decide it's time to involve a dermatologist to help keep patients on therapy?

Ms. Archambault:
Yeah, I think prevention is key. So in talking with families from the beginning when the medication is prescribed, I recommend gentle cleansers, short lukewarm baths or showers, and unscented soaps and thick moisturizers. Moisturizing is key. Many times, the patients will have dry skin, and having baseline preventative moisturizing is very important. Likewise, for photosensitivity, which can worsen the rashes or set them off, sunscreen SPF 50 or above is very important and recommended as well as some protective clothing. In terms of baths, I originally was a skeptic in terms of bleach baths, but I have become a fan. It not only reduces the incidence of secondary infection, but it also reduces the inflammation in the skin in general.

In terms of treatment strategies, I have patients continue those moisturizers, bleach baths, gentle cleansers, and things. But I also will prescribe a low-dose steroid cream like hydrocortisone for mild rashes anywhere on the body, including the face. I'll also prescribe a mid-potency steroid cream not to be used on the face, but on more significant rashes on the body. And I will also prescribe clobetasol or a higher-dose steroid solution specifically for pustular lesions on the scalp.

Generally, if the cutaneous manifestations are grade 1 or 2, I will manage them myself with the plan that I outlined. But if the adverse effect is either to a point where I don't feel that management is effective or it's grade 3 or 4 or more significant, then I will involve a dermatologist.

Dr. May:
Now, beyond cutaneous adverse events, MAPK inhibitors can also be associated with gastrointestinal, ophthalmologic, and cardiac toxicities. When those arise, Ms. Raber, can you tell us how you work with other specialists to manage these patients and how you balance toxicity management with the potential benefits of continuing therapy?

Ms. Raber:
We do our standard surveillance as recommended depending on the drug that's being used. For example, for the cardiac toxicities, sometimes an echocardiogram will show a lower ejection fraction. But we found—and this was news to us before we used these agents—that that's a subjective number and that often when it's evaluated by a cardiologist and when the patient's evaluated and then their echocardiogram is evaluated, that number is revised because it's more on a technician level. So that can be really helpful to understand, is this truly a toxicity or just the method with which the test was run? So reacting without reaching out to the specialist can sometimes be detrimental to a patient, so we really try to engage if we are going to make a change based on an echocardiogram, for example. And then we partner with them given the information on whether this is a recommendation to dose reduce or do something else for this specific patient.

For the other specialists as well, we found, especially with ophthalmology, that it's very helpful to have a baseline exam so that you understand where the patient's starting from. You know, patients often enter into these treatments being treated previously with several other different agents, and potentially, there are tumors affecting their vision depending on the location. Or maybe they had hydrocephalus, so they had deficits related to that. So having this baseline with ophthalmology to really understand their baseline exam gives us the advantage and the relationship with the provider to get patients in quickly if we are concerned there's something changing—could be a toxicity from medication or an indication that something was happening with the tumor. So having that good baseline where they know the patient and we can have a conversation with them is really helpful.

As far as the GI toxicities, this is again a place where for many of these, as you're hearing, if we can know about them quickly and react to them quickly, they tend to be easier to manage.

Dr. May:

For those just tuning in, this is *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Ms. Bridget Archambault and Ms. Shannon Raber about evidence-based strategies for addressing adverse events associated with MAPK inhibitors for pediatric low-grade gliomas.

Now, let's shift our focus to patient and family counseling. Before initiating treatment, Ms. Archambault, what conversations do you have to help families understand what they can expect, including the potential benefits and adverse events, so they feel prepared and supported throughout their care journey?

Ms. Archambault:
Yeah. In recommending treatment and obtaining consent for treatment, I think it's very important to be transparent with the family. I want them to know what I know. So I talk about the benefits, including time to response, whether we expect the tumor to shrink or stay the same, and what the data is supporting that. And then I also talk about the potential side effects and what their life can be like, what they can expect, what we can plan for in advance, and that they may need to respond to side effects to manage treatment appropriately.

Dr. May:
After we explain what families can expect, they often wonder what happens if treatment needs to be stopped. Current evidence suggests that rapid rebound growth can occur within weeks to a few months of discontinuation, even if the tumor initially responded to treatment. Given that possibility, Ms. Raber, how do you talk to families about the importance of recognizing and managing adverse events early so they can remain on therapy whenever it's safe and appropriate?

Ms. Raber:
Whenever we start these treatments—I think we both do this—we emphasize not to be defeated if there are toxicities and that we can often find that individualized regimen for their child or for themself as a patient and find that right symptom management plan. There's no cocktail or regimen that works for every patient, and it's finding the right balance for what they need and then helping them to stay on treatment. So I encourage them to reach out right away. I think this really highlights the need for a multidisciplinary team where you have nursing; you have people who are answering that phone who are going to be able to react and have systems in place for what to employ if needed and if patients are reporting symptoms.

Dr. May:
And, Ms. Archambault, I have one final question for you before we close. When a patient restarts MAPK inhibitor therapy after discontinuation, whether it was due to toxicity or rebound growth, what do you typically see in terms of adverse events the second time around? Do the same patterns tend to recur, or does anything change about how you monitor and manage them on re-challenge?

Ms. Archambault:
I think it depends on whether they're restarting because of toxicity or because of discontinuation of therapy and now subsequent rebound growth. For toxicity of therapy, obviously the therapy was discontinued because of an adverse effect. So whether you're restarting at the same dose or a lower dose, you are likely to expect some version of these side effects that they had previously. Obviously, if you're starting at a lower dose, hopefully that adverse effect will be less significant and more manageable, but it is likely to show up again.

And then if patients discontinued therapy because of treatment response and they took a break from therapy, again, it depends on what happened the first time. I don't necessarily expect new side effects right away, but if they had some adverse effects in the first month or two that got better the first time, I would expect that probably to happen.

Dr. May:
As those final comments bring us to the end of today's program, I want to thank my guests, Ms. Bridget Archambault and Ms. Shannon Raber, for joining me to share adverse event management strategies to support long-term treatment persistence in pediatric low-grade gliomas. Ms. Archambault, Ms. Raber, it was great speaking with both of you.

Ms. Archambault:
Thank you, Dr. May.

Ms. Raber:
Yes. Thank you.

Announcer:
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