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Real-World Cases in Pediatric Low-Grade Glioma: Exploring Targeted Therapies

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:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and joining me to share real-world patient cases in pediatric low-grade glioma care are Drs. Angela Waanders and Ashley Margol. Not only is Dr. Waanders the Section Head of Neuro-Oncology and the Director of Precision Medicine Oncology at Lurie Children's Hospital of Chicago, but she's also an Associate Professor of Pediatrics at Northwestern University Feinberg School of Medicine. Dr. Waanders, thank you for being here today.

Dr. Waanders:
Thank you.

Dr. May:
And Dr. Margol is the Director of the Brain Tumor Center and Neuro-Oncology Program at Children's Hospital Los Angeles, as well as an Associate Professor of Clinical Pediatrics at the Keck School of Medicine at the University of Southern California. Dr. Margol, it's great to have you with us.

Dr. Margol:
Thanks for having me.

Dr. May:
Before we dive into our cases today, let's briefly level-set the available targeted therapies for pediatric low-grade gliomas, and in particular, those with BRAF fusions, since our first case will focus on these mutations.

Dr. Waanders, can you tell us about these options and how you generally think about selecting treatments across patient profiles?

Dr. Waanders:
In 2025, we have two different regimens as targeted treatments that are FDA-approved for pediatric low-grade glioma. So I think that has changed how certain practitioners think about, strategize, and think through lines of treatment. BRAF V600E low-grade gliomas—with the publication and FDA approval—has changed that landscape, and more providers would consider that as first-line. One difficulty with that class or with treating BRAF V600E tumors is the higher risk of rebound progression or addiction to the pathway.

So this newer class of drugs is targeted inhibitors. They are trying to decrease the increased signaling due to the mutation-specific burden of the low-grade glioma. So we have BRAF alterations, predominantly BRAF fusions, we have BRAF V600E, and then there are classes of FGFR alterations, CRAF alterations, and some even rarer. So in the 2025 landscape, especially for second-line treatments and beyond, how we're thinking about those are: Do we know what your genomic alteration is? What is your age? What is your baseline function? Can you swallow a pill? Does this family have the ability to give medications multiple times a day? And how will someone see and perceive themselves?

So in the current state with the targeted inhibitors, we have mTOR inhibitors such as everolimus. There is sirolimus, but mostly, we choose everolimus. For the MAP kinase pathway, we have a whole class of MEK inhibitors. We have the combination trametinib and dabrafenib. And then, another game changer has been, in 2024, when tovorafenib became FDA indicated or approved. So another practical measure we may also consider is, depending on your insurance or lack of insurance, what can we actually prescribe you and

get to you?

So I think those are all of the different considerations when we're thinking about the practical treatment in the current era for pediatric low-grade gliomas.

Dr. May:
Excellent. Thank you, Dr. Waanders.

With that foundation, Dr. Margol, can you walk us through a recent case of a child with a BRAF fusion and how you determined which therapy to use, when you initiated it, and how long that treatment continued?

Dr. Margol:
Sure. I actually have a really interesting case. So I take care of a 6-year-old who initially presented to us because her parents noticed her balance was a little bit off. They thought maybe her vision was off. She was running into things and complaining of occasional headaches and some fatigue. And she had been seen a couple of times by eye doctors who noted that her vision wasn't great; they had given her prescription glasses, but the family—as parents often are correct—noticed that maybe something else was going on. So she was brought into our emergency room. She ended up ultimately having an MRI, which showed quite a large suprasellar mass. Not surprisingly, she had some obstructive hydrocephalus as a result of that mass. And because we always do an MRI of the brain and the spine, we found another nodule at the level of about L2.

And so the concern was, is this a low-grade glioma or is this a germ cell tumor given the fact that there was a metastatic focus? So we did a workup for germ cell tumor, including serum and CSF tumor markers, which were both negative. And so we ended up doing a biopsy and discovered that this was, in fact, a low-grade glioma with a BRAF fusion.

Here, we still use conventional chemotherapy as frontline, and so that's what we did for her. She got carboplatin and vincristine, and she had a nice radiographic response. Actually, at about 6 months, her tumor shrunk. She came off therapy, and about 15 months after completing therapy, her MRI showed radiographic progression. And so then the question is, when do you treat? Do we treat just on radiographic progression? What about her functional outcomes, especially her vision in this case?

So when thinking about what to treat her with, it's a conversation with the family. And so the conversation was, do we use tovorafenib, as it was FDA approved by that time? Or do we consider a MEK inhibitor? And so we presented both options to the family, went through the side effects of both, pros and cons, dosing, profile, etc. Ultimately, the family decided to go with tovorafenib. The main reasons for choosing tovorafenib were the once-weekly dosing. Like I said, she's 6, so not the easiest age to get a kid to take a daily or twice-daily medication, so the once-a-week dosing was a big benefit for them. They were also hesitant about the potential cardiac toxicity of a MEK inhibitor, so that was another reason for their decision.

One thing that I had brought up with them, obviously, was the concerns about growth velocity delay on tovorafenib. Six is an interesting age to consider that, and it was possible that she wouldn't grow while on therapy. But they were less concerned about that at this age, and so again, after weighing the risks and benefits, we went with tovorafenib, and she continues on tovorafenib right now.

Dr. May:
And how about a case involving a child with a BRAF V600E mutation, Dr. Margol? What factors influenced your therapy selection and initiation timing?

Dr. Margol:
When we think about patients with low-grade gliomas that harbor BRAF V600A mutations, I might differ from some as I actually really like to use monotherapy. I was thinking about a patient that I have now who we initiated therapy with dabrafenib quite a while ago, so this was before the FDA approval for dabrafenib and trametinib. And he did quite well. He had a really nice response and stayed on therapy for about 2 years with pretty minimal side effects.

Then, he came off of therapy and remained off therapy for another 2 years. I think it was at about that 2-year mark where he did have radiographic progression. And this was another patient with a suprasellar tumor. He had some visual impairment, again, so the threshold for these patients is lower when we think about when to treat. And so he had radiographic progression, I think, on two consecutive scans, so I felt like at that point, it was time to consider retreatment, and I retreated him with dabrafenib. Again, just dabrafenib monotherapy, and he's actually been on therapy for about 3 years now, and his tumor and visual acuity have remained stable on treatment.

Dr. May:
Turning to you now, Dr. Waanders, optic pathway gliomas often present difficult decisions as well, so could you share a case that demonstrates how you approach therapy timing, selection, and duration for these patients?

Dr. Waanders:
So when we're thinking of optic pathway gliomas, the question is, is it limited to one eye? Does it cross the chiasm? Is it limited to two eyes? Does it involve the suprasellar region and have extension into the hypothalamus and pituitary area?

Two different patient cases. One who had limited just to the chiasm, kind of interesting radiographically. It looked like an optic pathway glioma, but it was a little strange—not completely characteristic. But we knew we could not biopsy. So that's another key factor when we're thinking about optic pathway gliomas, especially if they're limited to just the optic pathway. If a patient has normal vision or pretty high functioning vision, we often will not biopsy those tumors and will treat empirically.

I am also at an institution where our standard of care is chemotherapy upfront as first-line, and so that patient started on carboplatin vincristine and had stable disease; he was able to have stable function, and his visual outcomes were stable. He went off of the planned treatment, and about 3 years later, he started to have radiographic progression. So similar to what Dr. Margol had presented, we had a couple of scans in a row that gave us concern. We followed vision at the same time. Vision was initially stable, and then there was a one-line decrease with the second radiographic progression.

In that patient, the tumor was still limited to just the optic pathway. So we still treated empirically. We did not biopsy and did not get the genomic alterations, and so we selected trametinib. This patient remains with some slight radiographic improvement and with stable-to-improved vision now over a year later on trametinib.

Another scenario with an optic pathway: a toddler whose vision was a little bit difficult to ascertain. The tumor was a little bit more classically looking radiographically, but it was still limited to the optic pathway, so nothing to biopsy. We treated empirically with carboplatin and vincristine. Towards the end of the chemotherapy, the patient did have some adverse reactions, so we ended up having to stop treatment a little bit early for fevers that persisted every time we gave chemo.

That patient was stable for about 18 months off of treatment, and then we saw radiographic progression, but outside of the optic pathway fields. So it started to have unilateral growth asymptomatic in the right thalamus. We chose to biopsy that lesion and identified a BRAF V600E mutation. And so in that scenario, biopsy—getting tissue so we would know what we were treating—was feasible. Vision was fine, and the patient didn't have any adverse events after the biopsy.

We gave the family the options of dabrafenib trametinib as well as tovorafenib; both are viable options, and both are FDA approved. After talking about the different potential side effects at length, that family also did choose tovorafenib because of the once-a-week dosing.

They are not a family that will tolerate side effects, so depending on rash and response, we do have them poised that we can trial or go to the other treatment option if needed. But I think the most important thing with optic pathway tumors are, can you get tissue safely without affecting vision? What is the vision like? How large is the tumor? And how quickly do you think vision will deteriorate? And if vision has already deteriorated, how quickly do you need response?

Dr. May:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Drs. Angela Waanders and Ashley Margol about patient-centered strategies for managing pediatric low-grade glioma.

Now, Dr. Waanders, if we switch gears a bit and focus on managing common adverse events, what proactive strategies do you use to help patients stay on treatment safely?

Dr. Waanders:
I think it depends on the class of treatments, if we're talking about routine chemotherapy regimens versus targeted treatment options. The best way, though, is by being very proactive very early on if you're starting to see a side effect to be able to manage it.

For the targeted treatments, there are some same types or overlapping potential side effects. They can affect how someone feels, how someone looks, or different organ functions. Obviously, the most severe are the ones that affect organ function, like decreased cardiac function, which has been associated with some of the MEK inhibitors. However, you don't want to discount that appearance can mean a lot, and if you have a teenager who does not want their hair to turn white like mine or who cannot tolerate acne or significant rash, being very proactive with the treatment options as well as the discussion of the potential side effects is key. And if you have multiple options available, talk with both the parents and the patient about what is most important to them in terms of potential side effects.

And then, just closely monitor and be very proactive, especially with the dermatological side effects. For the acneiform lesions, treat that very aggressively upfront or any of the other rashes. One of the management options that we've learned from our dermatologist is actually diluted bleach baths. The first time I heard about it, I thought it was a little crazy. But there is solid hard data, and it does help to

prevent some of the dermatological side effects that are more difficult to treat once they manifest.

Dr. May:
And when you're considering therapy discontinuation, Dr. Margol, what factors guide your decision, and how do you monitor patients after stopping treatment?

Dr. Margol:
Yeah, it's always difficult to decide when to stop. I think a lot of our decisions are based on trial data, so in the vast majority of clinical trials, we gave patients therapy for two years. So that timeframe kind of still sticks with us when we're talking about targeted therapies. But really, the things that we take into consideration are, how well is the patient doing from a response standpoint? So that's a functional response, right? Are they having improvements in their function or is their function stable? Is their function worsening? And then, obviously, pairing that with radiographic evidence, again, either of response stability or progression.

So taking all those things together is how we make our decision. I will say one thing I look at really closely is if the patient's continuing to have any evidence of response at all, I'll keep going—kind of with this idea that you're trying to get the most bang for your buck with the therapy that you're on. So I think that's something that we pay close attention to. But obviously, the flip side to that is, what are the toxicities that the patient's experiencing? So if a patient's tolerating the therapy really well, that's one scenario where you could potentially consider continuing. But these are real toxicities. As Dr. Waanders mentioned, they have real physical effects as well as psychosocial effects. I don't have a hard and fast rule for when to stop, but I think taking all those things into consideration and treating each patient individually is really important.

Thinking about how we monitor patients after we stop therapy, again, it's that dichotomy of looking at patients' functional status as well as their radiographic status. So we'll continue to get disease evaluation monitoring. We'll do MRIs every 3 months to start off with, at least for the first year while pairing those with functional assessments. So we make sure we do a great physical exam for patients that are at risk for vision changes or vision loss and pair that with an ophthalmology exam. And also keep a really close eye on their growth, both from an endocrinologic standpoint and for those patients who are on tovorafenib.

So I think when you take your patient off, it's really important to continue monitoring them to make sure that their disease isn't progressing, but also to make sure that any toxicity that they did experience resolves.

Dr. May:
Lastly, coming back to you, Dr. Waanders, how do you work with the broader care team to set expectations with families, especially when it comes to anticipating and managing side effects over time?

Dr. Waanders:
With low-grade gliomas, I think there is a unique factor in this in that these are not malignant tumors. And as we're thinking about side effects and managing those and going back to the previous question of when to take someone off of treatment, we want to make sure that the treatment is not worse than the disease and that we're treating the patient, not just the MRI image.

The care teams that are often involved, especially because of where low-grade gliomas tend to occur anatomically, are endocrinologists. Neuropsychology is also very important, especially since many of these children are so young or could have their vision already affected. A new field is cardio-oncology because many of these drugs may affect heart function long term. Survivorship is really important too as we hand these kids who are able to stay off of treatment for several years to our survivorship partners.

And then one aspect too that I think is important to mention is that both Dr. Margol and I practice in tertiary refer centers with a number of different subspecialists available who also have the breadth of experience in helping us manage these side effects. So for our colleagues who are in smaller centers, who may not have a neuro-oncologist or who are just starting to treat using some of these newer agents, I think as a community, we need to create more handouts and more information. There's also a number of really good clinical care guidelines on the adult side that can get translated into the pediatric side. So all of the ancillary support specialists but also self-education if these are drugs that you are not familiar with is really important. And then also knowing when to reach out to other specialists.

Dr. May:
With those key strategies in mind, I want to thank my guests, Drs. Angela Waanders and Ashley Margol, for joining me to share real-world patient cases that demonstrate how we can treat pediatric low-grade glioma. Dr. Waanders, Dr. Margol, it was great having you both on the program.

Dr. Waanders:
It was my pleasure. Thank you for asking.

Dr. Margol:
It was great being here. Thanks.

Announcer:
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