Targeting the Pathway: Evolving Roles of MEK Inhibitors in NF1 Associated Plexiform Neurofibromas

CEC Podcast Transcript

Jaishri Blakeley, MD:

Afternoon, good evening. My name's Jaishri Blakeley, I am delighted to welcome you to the "Targeting the Pathway: Evolving Roles of MEK Inhibitors in NF1 Associated Plexiform Neurofibromas." Today's program is supported by an independent educational grant from Alexion Pharmaceuticals and supported by Creative Education Concepts, an award-winning accredited provider of continuing education. I am delighted to be accompanied by world leaders in these topics, who I will introduce briefly, and we will be providing our opinions about the data published to date and how we use these agents in our clinical care. So you see that first of all, the Society of Neuro-Oncology has reviewed and approved the symposium, and it has been through all of the appropriate review for accreditation. These are the types of accreditation that have been approved if you would like to apply for and receive your accreditation. And one of the things that will happen is we will briefly mention some agents used to treat plexiform neurofibromas that are not yet FDA approved, but we will focus on the two FDA-approved agents.

So again, I'm Jaishri Blakeley, enough about me. I am delighted to be joined by Dr. Angela Hirbe, associate professor of medicine and pediatrics director, Adult Neurofibromatosis Clinical Program at Washington University School of Medicine, St. Louis. And by Dr. Darren Hargrave, so many initials, so many abbreviations. He's very honorable and he is the clinical professor of pediatric neuro-oncology, University College London, Great Ormond Street Institute of Childhood Health in London. So we all owe him a great thanks for coming all this way. These are our disclosures, please feel free to review them. And let's move on to our learning objectives. First, we will assess the neuro-oncologic features of NF1, including the tumor types and neurological signs and symptoms that may play a factor in your decision making. Then we will pass along to Dr. Hargrave who will talk about integrating MEK inhibitors into the management of NF1-associated plexiform neurofibromas; first in pediatric patients, and then Dr. Hirbe will discuss adult patients. And then we will close out talking about the need for interprofessional care and care plans for people with NF1 across the age continuum.

Ready? Buckle your seat belts. Okay, so I'm going to start us off and I'm going to talk about the neurofibromatosis. And collectively, the neurofibromatosis are three conditions, NF1, NF2 schwannomatosis, and all of the other schwannomatosis. And when I say all of the other schwannomatosis, we have two named schwannomatosis, LZTR1 and SMARCB1. And suffice to say, they're wildly rare but very important, we can have a different session about that. NF2 schwannomatosis is entirely unrelated to NF1, that's why it was recently renamed to NF2 schwannomatosis because really in that condition NF shouldn't be in the name at all, but we can't change 200 years of history.

Today we're going to focus on NF1, which is very common, about one in 2,600, one in 2,800 people, equal prevalence around the world in male and female, and multiple manifestations. These manifestations show up at different times across development. NF1 is in fact a tumor predisposition condition as well as a neurodevelopmental condition, so you can see that things show up for our patients at different stages in their development. And when you're taking care of somebody with NF1, the reason we're all up here, is there are different things we have to focus on when they're young, when they're in transitioning adolescents, young adult, and in later adulthood.

The diagnostic criteria are listed here for any board exams you might be taking. The big thing to say is that we revised the diagnostic criteria in 2021, and all we added is that ophthalmology is really important. There are more ophthalmologic findings that will help distinguish NF1 from other RASopathies for example, and genetic testing is really important. So please do not hesitate, do what you can to get genetic testing, particularly in our youngest patients, but also sometimes we see adults who present because their child was diagnosed and they don't know what they have. Genetic testing is really helpful.

Just to give you a flavor of the kinds of things people who are living with NF1 are up against, on my left, oh your left too, on the left-hand side of the screen are some manifestations that won't kill a person but are important to the patient. Cafe au lait macules, that top right area, oops, so sorry, and Lisch nodules have no medical consequence, they're not associated with severity, they don't need any intervention, they're just notable. The middle two images are cutaneous neurofibromas and glomous tumors. Cutaneous neurofibromas happen to more than 95% of people living with NF1. The people who have them hate them, they want you to fix them for them, but they don't have cancer potential. Glomus tumors are very rare, probably 15% of people with NF1, but cause horrible pinpoint pain under the fingernail, and you're a hero when you diagnose it. And then that bottom right is for the vasculopathies of NF1, which are extraordinarily rare but very important because they can lead to recurrent stroke and other vascular events in the periphery.

On the right-hand side of the slide are things you really have to know about because diagnosing them early, the appropriate intervention for treatment really does make a difference in outcome. And those include the low grade gliomas, including the optic pathway gliomas. Those are images of what they might look like on MRI. Today is not about optic pathway glioma, suffice to say about 20% of children with NF1 will have these, and most of them will not need treatment. So please read up on why that's true. The middle two images are of other gliomas that happen in the parenchyma, often in adolescent young adults or older adults.

The one in the brainstem is in fact a glioblastoma, as poor of a prognosis as you might expect. And the one that's in the posterior parenchyma is a ganglioglioma, as good of a prognosis as you might expect, but certainly needs treatment for all the reasons a ganglioglioma needs treatment, like seizure predilection. And then a dramatic example of diffuse plexiform neurofibroma, you're going to hear a lot about plexiform so I'll move along. And the bone manifestations absolutely need to be, we have to be aware of them because scoliosis is in fact quite common, up to 50% of people with NF1, and can progress very rapidly in childhood and adolescents. The bone dysplasias are very rare but can cause a lot of morbidity.

So one of the tremendous gifts of working in the NF field is to work with patient advocates and partners in care like Renie Moss, and you can read all about how amazing she is. She has an actual whole career, and she's a marathon runner, and she's a mom to two kids, and she's a tremendous advocate for people living with NF1 and teaches us a lot. So let's hear a little bit from her about accessing care in NF.

Renie Moss:

The challenges of accessing a neurofibromatosis clinic or a clinic that is well-versed and experienced in neurofibromatosis care, access to specialists that may be needed in that continuum of care, is very, very hard in our country, in the United States specifically. We were very fortunate when we received our diagnosis five minutes away was one of the best NF clinics in the country. So it was not our experience, but in my 10, 11 years of managing this with my family and engaging with parents and patients in the NF community, our experience is very unique. Most families do have to travel at least some distance, sometimes a long distance, to access the

care they need. That can affect your job, that can affect your employment, that can affect your school, that can affect your pocketbook, your finances.

And we're also a middle-income family with insurance, not everybody has that ability. So if you need an MRI and you're four hours away, having the ability to do that but then having to go back to get the results of that, or having to come do blood work, or a scoliosis scan, or a DEXA scan, if those appointments can't be coordinated that's a very expensive, both time and financial, commitment for that patient or that family to be able to travel back and forth and do that. And with NF1, because there are so many learning disabilities and sometimes multi-generational diagnoses, the ability to maintain successful employment is sometimes a challenge. So you add the distance and the financial toll it takes on a family to be able to access that care, along with the ability to maintain employment, to be able to do that it is a huge, huge stressor and frustration.

Jaishri Blakeley, MD:

So when you hear Renie talking about all of the issues of accessing care and insurance in particular, that might be a US problem, but the need for multiple appointments, and multiple different specialists, and coordination of all that is a universal problem. Okay, so I am going to ask Dr. Hargrave here, because I'm an adult neuro-oncologist so I have no business taking care of children, so I'm going to ask him to please comment on this child who is a seven year old male, has some mild learning difficulties, a little bit clumsy, but mostly he's been doing great. And at his annual physical examination he was found to have the skin markings that could be consistent with NF1, including some soft nodules, like cutaneous neurofibromas, and then his ophthalmologic examination showed Lisch nodules so we think we're onto something.

So he's diagnosed with NF1 based on the clinical criteria, the parents do not have any characteristics of NF1. And then you see the rest of his examination, he has nine cafe au lait spots, they're greater than 0.5 centimeters, and he has the axillary freckling, some mild hypotonia, no scoliosis, and some visual spatial and processing deficits. He really had a very thorough exam on that intake visit.

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

Yes, thanks.

Jaishri Blakeley, MD:

So what would you recommend to do?

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

So thanks, Jaishri. So obviously I think it's pretty clear that Sam's been diagnosed clinically with NF1. So what would we do? Well it's important that Sam then has appropriate baseline investigations. Jaishri's already told you that there is a potential high incidence of optic pathway glioma, and we would screen for that with ophthalmic exams, so he needs to go on a comprehensive ophthalmic examination. We need some baseline to see whether Sam's suffering from any learning difficulties or any behavioral issues, and of course really to be able to get the holistic support and educational support if that's required. As has been discussed, obviously this is a genetic disorder. Although one can make this clinically, it'd be appropriate that Sam and his family are

introduced to genetic counseling to discuss inheritance and start to think about the implications, which could be family testing and for the future reproductive planning.

He obviously has some issues, so we want to actually get those therapy services for Sam, including occupational therapy, speech and language. And of course the family have got to come to terms with this new diagnosis, so it'll be appropriate to signpost for appropriate local support, such as the Children's Tumor Foundation in the US. And then Sam will start to be linked in with the local team and have an annual follow-up, really the start of NF1 surveillance. So regular neurological examination, as robust as the one he's just had, looking at his skin, ophthalmology, and looking at growth and development. Because we obviously want to detect things early, this is a heterogeneous disease, to actually provide Sam with the support to be able to deal with this condition with that multidisciplinary team.

So we're going to move on now to talk about one of the manifestations. So plexiform neurofibroma and how we manage that, what therapies we have. So as already been said, NF1 is a tumor predisposition syndrome. The dysfunction in neurofibroma stops the tumor suppressor function, which means that you get an overactivation of the Ras/MAP kinase pathway, which actually drives these various entities which may or may not occur in an individual. So we've already discussed that you could develop a lower grade cutaneous dermal neurofibromas occurring, really in the second, third decade of life. Plexiform neurofibroma, which we'll talk about in detail and optic pathways in low-grade gliomas as we've said in about 20%. However, unfortunately for Sam, in adulthood with there are cancers that these patients may suffer from, so we need to be looking and trying to detect for those. So malignant peripheral nerve sheath tumors, which can arise from plexiform neurofibromas, more malignant gliomas, but then breast cancer in the adult population, these rarer tumors, and has already been mentioned these neuroendocrine tumors, and also some sarcomas.

So focusing on plexiform neurofibroma, we know that about 50% of patients have these. We think they're congenital but they may manifest later in life or later in childhood. And the natural history is that their growth is from an early age, but can continue all the way through adolescence and into adulthood, although usually slowing down. They arise from the neurovascular bundle, so they can be very infiltrative. Due to their location they can give rise to a lot of morbidities from major organs, and potentially can be life-threatening. Most patients who have a plexiform are going to have more than one comorbidity, and the most common things that patients will suffer from will be pain, disfigurement, and possible motor dysfunction. And obviously the location makes a huge difference, so this could also affect vision, could have impact on the airway, and bowel and bladder function as well.

Generally, symptomatic plexiforms will probably be larger than asymptomatic, but you can have a mixture of both. And these are benign entities but they can progress through becoming atypical neurofibromas. And there is a lifelong transformation rate of between eight and 13%, and therefore this is a major part of surveillance. So when we're thinking about plexiform management, we need to look at this in a holistic position. Not every plexiform is going to need to have an intervention such as medical or surgical therapy. And the factors that govern that are really going to be the age of the patient, the natural history of this, the location, the present or impending symptoms that are related to where that comes from. But it may well be that we observe or we provide symptomatic supportive care, and many stable tumors will not need to have medical or surgical therapy, but when they do of course we need to have very specific goals about what we're trying to alleviate, and also thinking about the kind of risks and side effects of any therapy.

So the two major management strategies when we have to intervene are surgery and medical treatment. And in order to know which of those we have to be thinking very individually about the patient, we need to be comfortable that any growth or change in the character is not due to malignant transformation and rule that out, which may be appropriate imaging with MRI, with PET imaging, or biopsy. And we must stress that the current medical therapy is not actually preventing that malignant transformation, so very important that we're aware of what we're treating. But if we do feel that we've got a symptomatic plexiform the first question will be, can surgery, which was our traditional treatment, play a role? We know that probably less than 15% can be completely resected, but there may still be a reason cosmetically or functionally for debulking surgery.

But increasingly, we have medical therapy, but it comes with its own issues. This could be access to medical therapy, this could be the side effects, could be the monitoring, and therefore we need to actually really consider very carefully about who to treat, not to treat, and with which modality. We should also say that these therapies are not mutually exclusive, it may well be that we go for an observation, a symptomatic, we may use surgery, we may use medical therapy, and therefore you really need to be thinking about the individual, their particular symptoms, and the risk for that particular family in the balances in treatment. And therefore, it's really important to have a large multidisciplinary team.

So let's go back again to Sam. So Sam's now 10 years of age, is developing an enlarging diffuse swelling of the left jaw. This can be tender and is steadily growing. Due to the location and nature it's thought not to be resectable, but it's starting to unfortunately cause some facial asymmetry. An MRI scan's done and confirms that this is a plexiform neurofibroma. And over several years there's a continued growth, really exacerbating those initial features of some disfigurement. Starting to affect functions such as chewing and perhaps speech. And then Sam starts to develop neuropathic pain, which will be managed by the appropriate pain team, but when he's 13 or 14 it's really having an impact on his quality of life. And over the next year or so it's decided that this is a significant function, so we need to think about intervention.

So this diagram is really encapsulating the number of people and the number of disciplines that need to be involved potentially for these patients in order to help Sam and his carers to come to an informed decision about what would be the best treatment. And in this case, due to the location as we've described, surgery doesn't appear to be the right treatment at this time, and therefore medical therapy, systemic therapy is considered.

Jaishri Blakeley, MD:

Dr. Hargrave, before you move to talking about our medical therapy, can I give you some questions from our audience?

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

Of course.

Jaishri Blakeley, MD:

So in a growing tumor in a child what are the markers, the non-invasive signs of malignant transformation? Is it only growth of the tumor or are there other things you'd look for?

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

No. So an increase in growth, which is actually perhaps an increase in velocity from what's previously happened is key, but it isn't the only thing. So pain that is becoming quite acute, and actually used often very much a hardening, a firmness of those lesions. Those three things together make you clinically start to worry and suspect that this could be a sign of malignant transformation. It won't necessarily be that case, this can be part and parcel, but it's those three things, that constellation that would prompt as we've said, those investigations.

Jaishri Blakeley, MD:

And what would those investigations be?

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

So, well I think if you've not had a previous lesion obviously MRI imaging, but actually if you had you'd want to repeat that to actually look and see whether there are actually different appearances, characteristics. And then actually PET scanning may be useful in terms of either giving you the suspicion that this could actually be a malignant transformation, but also guiding a biopsy to confirm that.

Jaishri Blakeley, MD:

Got it. And then do you believe that people who have large deletions in their NF1 gene are more likely to develop MPNST?

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

I have to say I'm not being convinced by that evidence, I don't know about my two colleagues here. Angela, what do you think?

Angela Hirbe, MD, PhD:

I mean I think if we look at our genomic data, at least from the GEM consortium and then I'm thinking of the set of PDXs that Christine [last name unclear] and I have generated, that we would have sort of a disproportionate number of patients with the micro deletions. So I do think that there is that risk there, and I think it makes sense because you're also losing SUZ12 in addition to NF1.

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

But it'd be a risk factor rather than being definitive, that stratification.

Jaishri Blakeley, MD:

And I'm going to split the difference and tell you, the more I invest in trying to understand this the more confused I am, because it depends on that microdeletion, to your point, what part is deleted. So then you need to go back to our genetics colleagues and be quite specific about what was the alteration and the structural change. So microdeletion by itself is not a definitive risk factor, but if you have lost SUZ12 in that process, and if we actually could measure neurofibroma function in a person, we could quantify that perhaps so. But if

someone has a microdeletion you should think twice that maybe it's not a definitive. So please tell us how you might treat this patient.

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

So let's talk about targeted medical therapy. So we've already talked about the activation of the pathway, and really so far the medical therapy is based on MEK inhibition to target them. We have two approved for children, selumetinib and mirdametinib, where they can-

Jaishri Blakeley, MD:

Which can I just pause for a second?

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

Yes.

Jaishri Blakeley, MD:

That's like in five years we have two approved drugs for a rare disease that had nothing approved, so amazing. Carry on.

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

I mean it truly is a success story. And in fact, there are other clinical trials where other MEK inhibitors have shown the same sort of in class effect, but to actually have two approved on the basis of the data that we'll talk through. There are other medical therapies that have also been explored, we've seen activity such as a receptor tyrosine kinase, cabozantinib, but none of those are approved. And it does, approvals do vary across different jurisdictions and across the world.

So let's talk a little bit about that evidence. So selumetinib was first approved from the NIH SPRINT trial. This is a phase two study for children two to 18 years with a symptomatic NF1 inoperable plexiform that had no evidence of NPNST. This is an oral inhibitor dosed 25 milligrams per meter squared twice a day continuously. And the primary endpoint was using volumetric analysis, something was defined by the range criteria, looking at a partial response rate of 20% with these secondary endpoints. So 50 patients were in the phase two, the median age was 10, there was a slight male preponderance. The target volume of the plexiform median was 487 mils in this particular one, and there was a split between those that were progressive or symptomatic. And you can see the locations here. Again, the comorbidities suffered by these patients tended to be disfigurement, pain, and motor dysfunction, but you can see some patients had an impact on airway and vision as we've described.

So this is an updated slide where the phase one and the phase two population have been put together, and what this actually showed was that partial response rate was 70% and a durable response rate of 59%. Eight cycles or eight months was where you seem to get this response occurring, but the best response was up to 18 cycles, so really quite a chronic treatment. And in this updated data median progression-free survival was 88 cycles, so 6.7 years, many patients continued on longer. And you can see here from the Natural History Study, this is a non-randomized trial, the significant benefit that MEK inhibition had been shown in selumetinib.

So MEK inhibitors are generally well tolerated, we're really talking about grade one and two toxicities, those in brackets are grade three and four. There's some GI side effects that are usually well managed, but the major aspect is cutaneous side effects with rash and paronychia, hair changes. But these can be mitigated, but you really do need to actually help the patients overcome those. Usually asymptomatic CPK is quite common but does not normally need to have a specific dose adjustment. Fatigue I think is something that the patients do notice, and many of these low grades can have quite a chronic burden, so you will see dose interruptions and modifications, in some cases discontinuations. But again, with the right support many patients will be able to continue and take these medications.

These were the concerns from adult cancer studies where there was concern about retinol eye toxicity and cardiac toxicity, but really in children we've actually seen that those are very low grade, usually are not actually leading to discontinuation, but there may need to be a pause in treatment, and is usually reversible. This is the FDA approval warning so again, just talking about being aware of ocular toxicity, cardiomyopathy. And really this is informing the monitoring that we need to do when we're actually looking at these children.

So what about the clinical benefits? Well perhaps the most obvious was those patients that had plexiform related pain, and what we can see just using the pain NRS-11 score was that those patients after one year of therapy had a significant decline in their plexiform related pain, and actually in the longer term follow-up that continued. So this was of a major benefit. And you often see this occurring really quickly before you'll actually see volumetric reduction, but equally you can see it return when you actually stop. So there is a very specific mechanism of action that's occurring there, but can really get patients off long-term opiates, neuropathic agents, et cetera.

So for mirdametinib the data comes from the ReNeu trial, and so it's just been updating some of you perhaps in the last session. I'm just going to talk about the pediatrics. So again, an oral medication but this time twice daily, but actually on a three week and one week off schedule. Same primary endpoint of looking at volumetric reduction and a similar population, this time, actually 56 children, again median age 10, more balanced. The location of the NF was slightly different, but they also had pain and disfigurement as their major concerns. And here we see a waterfall plot, you can see that the 20% volumetric reduction has been achieved by 52% of patients, and many of those getting a deeper response. The target volume was slightly less, in this medium was at 99 mils, but actually very, very similar response is seen. And for the pediatric population, median reduction was 42% in that volumetric reduction.

And again, clinical benefit, significant benefits seen in the same plexiform related pain scores, but also an improvement in the pediatric total quality of life. So patients are deriving benefit. And when we look at adverse events, they're very similar in class, not really a major difference here. And again, in the FDA warnings precaution the similar AEs of specialist interest.

So Sam is now 19 years of age, has been receiving selumetinib continuously for the symptomatic plexiform, and has had benefit from tremor shrinkage, which is now stable, and the pain associated with this has also improved. So one of the questions is how long do you actually treat these patients for? And we'd like to ask you what would you do with the selumetinib with turning into an adult, been on this for a number of years now, so what would you recommend? Would you stop therapy, switch to a different MEK inhibitor, or stay on selumetinib? So Angela, so most people are going to stay on selumetinib, I guess backing a winning horse. What would you do in that situation?

Angela Hirbe, MD, PhD:

I think that's what I would do also. Before selumetinib got the adult approval, which just happened the other day, so before that one could have argued, and actually insurance companies were starting to try to force our hand at saying, well selumetinib is not FDA approved for adults, but mirdametinib is. Though I would see no reason to change a MEK inhibitor if somebody is doing well on that MEK inhibitor. And then I would still be very hesitant in a 19 year old or even somebody in their 20s in terms of just stopping the MEK inhibitor like you mentioned before, because of the chances of the pain coming back, and I think regrowth in that patient population. Whereas I don't worry so much about those things in older adult patients. So as we move along we'll sort of talk about that transition of care going from the pediatric setting to the adult setting.

Jaishri Blakeley, MD:

Literally pediatric to adult.

Angela Hirbe, MD, PhD:

That's right, a little handoff here. But we'll hear from Renie first.

Renie Moss:

So of all the questions I have to think about as a parent of children with NF, the transition of care to adulthood is probably the one that I am most passionate about and most ill-informed about because I'm in the midst of it myself right now. And what I would say to care teams or nurses that may be hearing my voice right now is do not underestimate the power of peer support and making sure that if you have the ability to connect your patients to those patient communities, it is so critical. It is very difficult to ask really questions that don't have black and white answers related to this because every family is unique.

And so hearing from your doctor or your nurse is one thing, but hearing from a peer who's been there ahead of you or is in the midst of it, the combination of those two things are so very important, especially when you may not have access to an NF clinic. There's a lot of online support systems, there's patient organizations that are very, very good about connecting newly diagnosed or families that are dealing with whatever the circumstance is.

So transitioning to adult care, it's hard enough transitioning a child that doesn't have neurofibromatosis to adult care when HIPAA issues happen, and power of attorney may be playing into it, and all of the different things that happen. So I learned a lot from hearing from other families, so before our son was turning 18, literally over a year ahead making sure that we were thinking about what that would look like and explaining to our son that I don't have access to your patient portal anymore unless you give me your login, which is going to be up to you.

Angela Hirbe, MD, PhD:

So as Jaishri mentioned earlier, the manifestations of NF1 differ in kiddos versus adults. And so these are things that we have to think about in terms of what providers need to be there to care for these patients as you're transitioning. I think there are certainly barriers that exist, and these are probably different depending on what country you live in. I think in the US in this space often there is sort of limited resources in the adult setting in terms of perhaps less access to social workers or case management. I think in general, in the NF space, we have

fewer adult providers than we do for peds, at least again in the US. The approach is different in a children's clinic versus an adult clinic, and in adult clinic a patient has to be their own advocate for their healthcare, the team is just a bit different. And again, insurance is an issue in the United States, perhaps not in other countries.

I think there's no perfect way, but just some potential things that can help are sort of talking about transition of care early, starting to try to assess patients as to whether or not they're ready to take on their own healthcare, again learning to advocate for this multidisciplinary approach. Sometimes I think it's helpful to try to schedule separate appointments to help with the transition of care, that's something that we do at our site. We have an amazing occupational therapist on the ped side who will meet with the patients after our peds providers to start going through this transition assessment questionnaire, and see if they're starting to get ready to be able to transition into our clinic.

I'm not going to read through these, but I think again it's just important to kind of understand and assess whether or not somebody is ready to transition, planning by making sure you have all of the providers that you need to refer the patient to in the adult setting so that there's no lapses in the care. And then I think handoffs are important, we need to talk to each other to make sure we know what issues a patient has so that they're managed appropriately. And then there are some different online tools that you can access if this might be helpful. So you can find these transition readiness questionnaires here and some other helpful information, both providers and things that you can give to families to help.

So with that, I'll move into discussing MEK inhibitors in the context of the adult patients, and we'll go through some of the data also with some cases, but we'll switch to a different patient. So Mary is a 45 year old female with a painful facial plexiform neurofibroma that's also causing significant deformity. The pain's similar to what it has been for years, so no new changing pain, and her MRI doesn't demonstrate concerning features of the tumor. So those are all important things for me to make sure that I'm not worried about this transforming. So we'll take a look at the ReNeu data first, so again this was the phase two open label study. We're talking about the adult patients here, again slightly more males than females, nice distribution of location of the tumors. Pain was really the predominant NF1 related complication, although disfigurement or major deformity also is in about half of the cases. Target PNs were progressing in about half of patients also.

So mirdametinib, two mgs per meter squared BID, this is dose three weeks on, one week off. And the primary endpoint was partial response, so greater than 20% volume reduction. So you can see here a waterfall plot that looks pretty similar to what we saw for the pediatric patients, and again similar to what we saw in the kids, the adult patients did report improvement in pain, as well as improvement in quality of life. And I think that those things are very, very important. In my mind, we're treating patients, we're not treating scans. In terms of adverse events, pretty similar. I think the biggest thing in the adult patients is the acne-like rash, and then diarrhea would be the most significant GI toxicity that we see. Increased CPK is also seen in a decent number of patients, and again like you said, not something that I think really needs to be acted on in most cases.

So as of just yesterday we now have two drugs that are approved for adults, and the selumetinib approval in adults came from the KOMET study, which was a phase three placebo controlled study. Again, NF patients with symptomatic inoperable PN. So if you look at the study schema here the primary endpoint was overall response rate by cycle 16. So patients were on that placebo for the first 12 cycles and then they were allowed to cross over to selumetinib if they were in the placebo arm. And so if we look at the waterfall plot and the swimmers plot here, again we can see nice response in terms of decreases in tumor volume, and these are durable responses in adults as well.

Adverse events, again pretty in line with what we would expect for a MEK inhibitor, so GI toxicity, the skin rashes, elevated CPK, I think fatigue. And I think in the adult patients we often see weight gain as being an issue as well. Again, looking at the pain scores, so the adult patients with selumetinib had decreases in their pain scores. Interestingly, there was some decrease in the placebo controlled arm too, although a more significant decrease in the patients who were receiving the medication. So again, we have two options here, we have selumetinib and mirdametinib. They're now both approved for pediatric and adult patients. They both have a formulation that is useful for patients who are unable to swallow pills, selumetinib has a sprinkle formulation, mirdametinib has a dispersible tablet with a grape flavor.

I think the one difference that you can talk about with patients that may matter to them is that selumetinib is continuous therapy, so there's no off week. For some patients they may prefer this, they're worried about missing doses and they don't want to have to think about when they're on, when they're off. For other patients they want to have a week off of therapy, which is how mirdametinib is dosed. There is no head-to-head comparison, there never will be, and there's no data necessarily for switching MEK inhibitors. Although I will say I have had some patients who started having worsening pain on a MEK inhibitor, we switched to a different MEK inhibitor, and their pain seemed to improve. But again, that's not formally studied, I think all of that is sort of anecdotal.

So we'll talk a little bit about sort of managing the toxicity that we can have with these therapies. So Mary receives mirdametinib, her facial tumor shrinks to approximately half of its original size, pain improves substantially, but she develops a grade four CPK increase. So back to the iPads, what would you recommend for this patient? Assess for symptoms, if asymptomatic continue therapy, B, switch to selumetinib, C, withhold until grade one and then resume at a lower dose, D, permanently discontinue, or E, continue irrespective of CPK increase? All right, I like that answer. Well I think, so here's the difference, we talked about this when we were preparing for this. I think there's a difference between what the technical recommendations are in the package insert and what I would necessarily do clinically. So I would agree with the 35% who said assess for symptoms and if asymptomatic continue therapy. I think the package insert technically says to withhold until less than grade one and resume at a lower dose.

Jaishri Blakeley, MD:

Could you say why you would assess for symptoms and continue if there are no symptoms, even if their CPK is 2,800?

Angela Hirbe, MD, PhD:

Yes. So I mean if there are symptoms then I'm worried that there's something that's actually going on there if they're having pain. But if not we know that you can get an elevation in this, and I don't think I've ever seen a patient who has had a symptomatic elevation in their CPK on a MEK inhibitor, I don't know if either of you have?

Jaishri Blakeley, MD:

I've never seen it. I tell my patients that they have to hydrate as if they're going to be withheld from hydration for five days before they go for their blood test, and then we don't see elevations. It's not a marker of a true biologic process, in my opinion. I do think we need to be cautious about that, and the thing I worry about is if they are not clearing the protein in their kidneys, if the kidneys can't filter then we'll cause renal dysfunction. If

I'm not seeing renal dysfunction, I'm not seeing muscle pain then I carry on, but I push the hydration. If they can't hydrate then we have a discussion about dose reduction.

Angela Hirbe, MD, PhD:

That's a very good point. And if you do an intense workout the day before you get your blood drawn that will also lead to an elevation in your CPK.

Jaishri Blakeley, MD:

Don't do marathons like Angie and then go get your CPK drawn.

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

We always say please don't go to the gym just before because it will just unnecessarily raise the alarm. But I agree, including children we really just can continue with these. It was different in the trials when we learned about, but when you've had that experience you have that confidence that you're really not going to lead to problems.

Jaishri Blakeley, MD:

Great. One more point, switching to selumetinib won't help you, a person who has elevated CPK will have elevated CPK. So independent of the MEK inhibitor it is an on target side effect, what you have to worry about is the kidney function.

Angela Hirbe, MD, PhD:

Very true. So this slide really just summarizes what we need to do to monitor patients. So physical exam, always important, always asking about their vision, although I've again never seen any visual toxicities from these medications. The skin toxicities are really what I worry about, every visit that should happen. An eye exam baseline, I typically will do these just annually, recommendations are every six to 12 months. And certainly if somebody has symptoms then we're going to send them back to optho. Echocardiograms to assess the ejection fraction, again at baseline. I do this every six months, I sort of try to do everything with imaging, which is why I picked the six month time point. An EKG is really baseline that is clinically indicated, pregnancy status, baseline and per institutional standards. And then labs, typically every three to six months. I have a lot of patients who come from far away so we'll have them get local labs at that three month time point and then again, getting everything when they come back to see me at that six month time point.

Jaishri Blakeley, MD:

Can I pause you here and address a question from the audience, which is how do we decide monitoring guidelines for people with NF1 who have plexiforms in general, and then how do you modify that when they're on a MEK inhibitor?

Angela Hirbe, MD, PhD:

How do I modify them by imaging, is that kind of-

Jaishri Blakeley, MD:

Whatever you would do.

Angela Hirbe, MD, PhD:

Whatever is, yes.

Jaishri Blakeley, MD:

So you have a 35 year old who you know has a plexiform, or five, how do you think about monitoring, and then how does that change if you have them on therapy?

Angela Hirbe, MD, PhD:

It's a very good question. So if they have a plexiform we will image probably every one to two years, or if somebody has a change in terms of their symptoms.

Jaishri Blakeley, MD:

Forever? Until they're 88?

Angela Hirbe, MD, PhD:

I probably tone things down as people get older, but in their 30s and 40s that's when I'm worried about an MPNST happening, and I think patients are pretty anxious usually as well. In terms of when somebody's on a MEK inhibitor then that changes, right? So we're monitoring them, so we typically will do imaging every six months in terms of looking for whether or not there's a response to that therapy radiographically. But one could argue that perhaps that's not totally necessary either because again, to think that I'm treating a patient, not treating their scans. When I am meeting with a patient and deciding whether or not to start them on a MEK inhibitor I'm talking to them about what it is that's bothering them, what do you want to do that you can't do, and then trying to see whether or not they're able to do those things. And whether or not they can come off of pain medication if they're on it is also, I think, an important measure of success, more so than I think what a scan shows.

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

Yes, that's exactly what we do. What is it for that individual that they want to achieve, and actually then we're trying to objectively measure that rather than the scan. We will do a scan as well, but it often will not correlate to that.

Jaishri Blakeley, MD:

And then I'm just going to add in, oh yes, please. So let me repeat your comment and just tell me if I have it correct, that you're hypothesizing that a person with NF1 and plexiform that goes on a MEK inhibitor may have different risk factors than a person who never entered that eligibility, and so that would argue for more frequent surveillance? And this is why this is so fun because I would tell you I don't care what the MRI looks like, I care what your reflexes look like, I care if you can control your bowel and bladder, I care if you get scissoring of your

legs when you're sleeping. And the MRI, where I practice where I do not have equal access to healthcare, might keep people from coming to see me because they end up with a $3,000 copay. My copay, $30. So I'm a lot cheaper than an MRI, and we can speak to the functional element of that, but it all depends on where you practice.

But I do think one of the important things you're raising and you were saying, we do not have guidelines about the appropriate surveillance because we don't have data that says if you get MRI every four months, or six months, or eight months, or 9.6 months, or whatever you want to say, we don't have anything that says when you do it at this interval you detect this much of disease change. So we each find something we're comfortable with your patient population, and then you have to navigate your healthcare system. What I love about a chart like this, you may not be able to achieve a chart like this, I cannot get an echocardiogram every three months, even if I offered my firstborn they would not let me have that. So when I'm putting someone on a MEK inhibitor I say, for now and for the next three years we are scheduling your echoes every six months. And if you cancel them that's on you, sister, because I can't get you another one. And we just have a negotiation about access to healthcare and how that matters.

But it's a really good point, we don't have guidelines for how to image. There are a lot of papers we've written with our opinions, like we're giving here. All opinions matter, they matter most when you've fleshed it out with the patient in front of you who's paying the copay and coming for the study.

Angela Hirbe, MD, PhD:

But they also don't always matter to insurance companies in the United States.

Jaishri Blakeley, MD:

Yes, this is true.

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

I'm feeling a whole lot better about the UK NHS system, I'd say.

Angela Hirbe, MD, PhD:

So our dermatologist also recommends that for the pediatric patients the bleach baths. For the adult patients I actually will start them on a tetracycline, usually doxycycline, 50 milligrams daily. So not like a full antibiotic dose but more of an anti-inflammatory dose. Start that at the same time that we start a MEK inhibitor, and usually by about three months we can stop the doxy and we really don't have issues with the rash.

Jaishri Blakeley, MD:

I learned that from you and it works really well, thank you.

Angela Hirbe, MD, PhD:

No problem. My nurse and NP are putting together a poster for CTF, they've been photographing our patients and documenting this.

Jaishri Blakeley, MD:

That's awesome.

Angela Hirbe, MD, PhD:

Paronychia I think is more of a pediatric problem.

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

Yes, I mean and it probably is the most tricky. I think it is the one where you get breaks recurrent. I mean we do quite aggressively get podiatrists or a surgical kind of debridement, and quite often that will actually give you a prolonged period of time for those selected patients.

Angela Hirbe, MD, PhD:

Yes. I've actually never seen that in an adult patients.

Jaishri Blakeley, MD:

I haven't either.

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

Yes.

Angela Hirbe, MD, PhD:

And then again, I think weight gain is something that I'm seeing in my adult patients who have been on MEK inhibitors for several years now.

Jaishri Blakeley, MD:

But I will say I usually am happy they've had some weight gain. They are often underweight, and so it's not been a problem in my experience.

Angela Hirbe, MD, PhD:

I have a couple patients that are unhappy about it that were not underweight, but I agree with you for the most part. And then some fatigue, although most of my adult patients tolerate this pretty well. And then the GI side effects, similarly I think I mostly see diarrhea in the adult patients, responds well to Imodium. And again, that usually sort of tapers off after a couple months as well. So I'm going to hand it back to you, Jaishri.

Jaishri Blakeley, MD:

Yes, thank you. So we have a summary slide that I'm going to go through, but there are some great questions here, and obviously really smart and experienced people in the audience, and we have a lot of unanswered questions ourselves. So let's start with the summary, which is I think you've got it now, that people who have the diagnosis of NF1 are at risk for tumors, both benign and malignant. And benign and malignant refers to

histology, not to quality of life. And we have good treatments for the histologically benign plexiform neurofibromas, they are up to 50% of people with NF1, they are heterogeneous as Dr. Hargrave mentioned, but they can have substantial impact on quality of life, neurologic morbidity, other organ morbidity, and unfortunately can undergo malignant transformation.

And I hope you heard from all three of us independently how scared we are of NPNSTs and how close we monitor for that. So my surveillance is not, I don't care if a plexiform shrinks, I really don't. If I put you on a MEK inhibitor I am not looking for shrinkage, I'm getting an MRI to prove that nothing scary is happening because the MEK inhibitor doesn't prevent the scary things. Unfortunately, wouldn't that be amazing if it did? Plexiform neurofibromas can be managed surgically, sometimes they should be managed surgically, but they always involve loss of some kind of function because plexiforms live inside of a nerve. So we just have to decide with our surgeons and our patients what type of that loss will be. If it will be a minor sensory deficit, no problem, if it will be a major neurologic motor deficit or bowel bladder, then we're talking about MEK inhibitors.

There are many clinical trials that we'll talk about in addition to our two approved therapies for adults and pediatric patients. And you heard about how important transition of care is, and I would argue it always has been, and it's always been fragmented, and it's going to take a lot to overcome that. My hypothesis is that MEK inhibitors are going to fix that because you're going to need someone to pick up the dosing and we're going to have to choose a date. We're going to say, okay, I gave you a 90 day supply, who's prescribing the next round? I have to find you an adult doctor. And so maybe this will be helpful. So we have plenty of unanswered questions, we're going to put these up here because these are also being asked by our participants. So let me start with you, Dr. Hargrave, can you predict who will and will not attain benefit with a MEK inhibitor? And if so, will you teach me how?

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

Yes, so unfortunately not. I think the most success I've seen is when people have genuinely got plexiform related pain, but the pain is often so complex it could be skeletal, there could be a psychological element, and of course then it won't work. But actually for those that do, generally speaking I'm fairly, I think I'm able to predict those, and you actually get the answer very quickly. But otherwise it is difficult to, and I agree with you, this is about the patient, not about the volumetric reduction.

Jaishri Blakeley, MD:

Dr. Hirbe, are there any research approaches that are coming up that might be biomarkers to say what person might benefit from a MEK inhibitor and what person might not?

Angela Hirbe, MD, PhD:

You know my passion here but, I mean I hope down the road. I mean as you know, we've been trying to use cell-free DNA as a way to monitor both treatment of plexiforms and MPNSTs. But I think another interesting question, and I think there's some work out of Northwestern looking at this too, is whether or not you could use sort of a liquid biomarker to try to predict who might develop a plexiform neurofibroma. So interesting questions, but I think it'll take some time to answer.

Jaishri Blakeley, MD:

Do you think people develop resistance to a MEK inhibitor? They're on it, it's working, they have pain benefit, they have tumor shrinkage, and now they don't.

Angela Hirbe, MD, PhD:

I mean potentially, but I think it's even more complicated than that because I still think that some of what's going on with the pain has to be modulating the tumor microenvironment in some way, and I don't think we really have the data to answer what's going on. So I don't know that it's resistance in the same way we think of resistance of a cancer cell developing, because I feel like it may be something that you can flip back and forth, whereas when cancer cells rewire it's sort of permanent.

Jaishri Blakeley, MD:

I totally agree. I don't think there is an intrinsic resistance of whatever the target cell is. By the way, we don't know the target cell for MEK inhibitors, but whatever the target cell is I don't think it develops resistance on treatment. But I do worry very much that there is a bad thing trying to develop when that happens, or that scoliosis is developing, or that they haven't been taking their dose. So then I check their CPK randomly, random drug check, if they go in without hydration and they don't have a high CPK they haven't been taking drug. Okay, and will you guys talk about how long do we need MEK therapy? And when you have a discussion with a patient or family, pediatric patient, adult about stopping do you think about weaning or do you just say, let's stop cold turkey?

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

So I mean I think the duration again, it relates to the natural history for that individual patient. For younger patients I have to say, because of the natural history we really are investing in several years if this is working for the patient, really going as you said up until 20s and possibly longer with the new indications, unless that risk benefit is lost. And obviously sometimes when patients become teenagers they themselves vote with their feet with compliance and you actually have a period of time. And then they can judge whether they actually prefer to be off or want to go back on, and sometimes they go back on from there. So for myself usually if this is effective I'm kind of talking to them that this will be a long-term treatment during childhood and adolescents.

Angela Hirbe, MD, PhD:

Yeah. In the adult space I think if they transition to me at 18 and they're on a MEK inhibitor or they're on a MEK inhibitor in their early 20s, I am hesitant to stop it because I think in that patient population, and I have tried it twice and I did see really rebound increases in pain. And in one patient when the neck plexiform started to, she felt it was growing again. Whereas the adult patients that I've had that are more in their 40s or 50s, some of them after a couple years of therapy have wanted to stop and see. And for those patients I have not had to restart a MEK inhibitor, they haven't had return of their pain.

Jaishri Blakeley, MD:

We have so many good questions, am I allowed to go on? Somebody wave if I'm allowed to go on. Okay, I'm going. All right, so two comments of people who've been using MEK inhibitors. One is that they have noted improvement in motor function, correction of weakness, and even improvement in scoliosis while someone's been treated with a MEK inhibitor. Should that be considered before we have discussions for surgical correction, Dr. Hargrave?

Darren Hargrave, MB.Chb (Hons), MD, MRCP, FRCPCH:

So I have to say I haven't seen an improvement in scoliosis, but I have seen an improvement in motor function for younger patients, obviously related to, I often think it's not the volumetric but there is a softening that actually occurs really quite quickly with these. When you can palpate it you notice that. And I suspect that that is having some effect on the internal pressure on the nerve that it's arising from, and that may lead to some recovery. I have to say scoliosis though, I think I would still be monitoring those patients and I'm not sure that I'd be banking on a mechanism preventing progressive scoliosis.

Jaishri Blakeley, MD:

Fair enough. I want to say I work at Johns Hopkins, we have a study where we're getting whole body digital images once a year. And we have a cohort of people who are on MEK inhibitors where we're following exactly this question, is there a change in curvature? I'm reading your mind and saying when someone has severe scoliosis and they have NF1, that turns bad very quickly. So those people need really close monitoring. When it's your conventional 10, 15 degrees scoliosis we have time to wait, but really be cautious with the people with a more than 20 degree curvature. Dr. Hirbe, for people who do not have benefit from a MEK inhibitor, what would you do instead if they're not getting the benefit you want? And do you think there is a molecular level to verify that the MEK inhibitor is working in that person?

Angela Hirbe, MD, PhD:

We don't have biopsies from these to sort of know are you hitting the target? And as you said, we don't even know what cell we're really looking for. So I'm not sure about the molecular way to measure whether or not a MEK inhibitor is working. I would say if I'm not getting benefit from a MEK inhibitor and surgery is really not an option, I'm usually working with our interventional radiologists, sometimes there is an injection that they can do to sort of try to help with the pain. That's sort of a temporary fix and every couple months they would be needing injections. And then there are now a couple other trials that we have going on-

Jaishri Blakeley, MD:

What? There are trials?

Angela Hirbe, MD, PhD:

Yeah. So the selumetinib drug, which is an antibiotic I guess approved in Europe, was found in a drug screen. And so that trial is open through the NF Clinical Trials Consortium. We actually have consented two patients now who should be starting soon. But I think looking to the next options is what we have. The selumetinib,

cabozantinib combo is supposed to open at some point. And more research is going on, so hopefully there will be other drugs that we'll be testing.

Jaishri Blakeley, MD:

I'm very sorry to the questions we didn't get to answer, we're all happy to talk to people afterwards. I'm going to wrap up now by saying the goals from this session were to have these smart, I can't remember what they are, something obtainable, reproducible-

Angela Hirbe, MD, PhD:

Specific, measurable, achievable, relevant in time.

Jaishri Blakeley, MD:

Thank you so much. So people who have NF1 do better in an NF1 center, at least for some consultation. And then we are so delighted, I run an NF center, it's a privilege, and it is an extra privilege to work with my patient's home providers and really have that partnership. They don't have to come to me all the time and we can share that care very well. No matter where that person is living, they need robust multidisciplinary care. There is no one expert in NF1, we need everybody working together. And to achieve that we really do need to be very conscientious about these transitions for our pediatric, adolescent, and young adults as they transition to the big scary world of adulting and help them get ready for that.

So I'm sorry you have to come up and talk to us after here to ask a question. There are additional resources at thececconcepts.com, and you can claim any one of those credits that we talked about at the beginning of the session to complete your CME requirements, here's some additional difficulty about how to get those. And with that, we'll say thank you so much, it's been a pleasure to be with you today.