Management and Multi-specialty Approach in the Evolving Treatment Landscape of Neurofibromatosis Type 1 Plexiform Neurofibromas

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Disclosure: Azizi has served on the advisory board for selumetinib for AstraZeneca and received honoraria by AstraZeneca for a lecture held at EANO 2021.

Acknowledgements: Writing assistance was provided by Eleanor Roberts, Beeline Science Communications, London, UK

Support: This article was supported by an educational grant from AstraZeneca.

Disclaimer: The opinions expressed in this article belong solely to the named interviewee.

Citation: EMJ. 2021;6[4]:32-35.

Interview Summary

Neurofibromatosis Type 1 (NF1) is a rare disease, occurring in approximately 1 in 3,000 people. Among the numerous manifestations of the disease, 30–50% of patients diagnosed with NF1 develop plexiform neurofibromas (PN). These are benign tumours that develop in infancy and childhood, differing in size, location (trunk, limbs, face, etc.), and growth rate. Treatment for PNs involves an evaluation by a multidisciplinary team (MDT) at an expert centre and most often involves surgical consultation depending on location, extent and growth of individual PNs, and patient-related factors. More recently, drug therapy with mitogen-activated protein kinase kinase enzyme (MEK) inhibitors has been included as a choice of treatment for PN. It may be used alongside, or as a replacement for, surgery if a symptomatic PN is judged as inoperable. The potential risk of malignisation (approximately 10% lifetime risk) also necessitates appropriate surveillance of PNs. In this article, Amedeo Azizi, Medical University of Vienna, Austria, spoke to EMJ about the current treatment options available for PNs and how these may evolve in the future.

INTRODUCTION

NF1 is caused by the inactivation of a tumour-suppressor gene that codes for neurofibromin. PNs are benign nerve sheath tumours, arising from nerve fascicles, which can also infiltrate adjacent tissue.[1] Symptomatic PNs most often occur in early infancy or childhood and may be disfiguring, impair motor function, or cause bowel or airway obstruction. Symptomatic lesions (with rapid growth, persistent pain, and motor dysfunction) may also be indicative of malignant transformation to malignant peripheral nerve sheath tumours (MPNST), which occur with approximately 10% lifetime risk.[2]

Treatment for PNs is co-ordinated in centres of expertise, housing a dedicated MDT. Alongside NF1 specialists and case managers, whether they are paediatricians, neurologists, or oncologists, the MDT should also include members such as experienced plastic surgeons, radiologists, and nuclear medicine specialists. Depending on

tumour location and extension, a MDT may also include speciality surgeons with expertise in, for example, neurosurgery, facial, abdominal, or thoracic surgery. Psychological support is also important, especially where the tumour (or the result of surgery) is visible and/or disfiguring as, explained Azizi, psychosocial issues often include problems with interactions with other children and schooling.

A risk-adapted approach to treatment is key, as some patients (e.g., those with NF1 microdeletions and extensive internal PN) can exhibit a more severe disease course.[2-4] Before any intervention, the NF1 specialist (and psychologist where feasible) meets the patient and family to discuss all possible options and implications. From age 5 years and even before, discussed Azizi, his team involves the child in consultations to discuss the potential benefits and adverse effects of different treatment options.

SURGERY FOR PLEXIFORM NEUROFIBROMA

Surgery is the bedrock of treatment options for PN and is currently the only potentially curative treatment.[2,4] Azizi recounted how some NF1 specialists argue that if a small child presents with an operable PN, no matter what the development might be, the PN should be removed to prevent further growth, related morbidities, and/or malignant evolution. However, there is no way to predict whether a PN will grow and, stressed Azizi, another strategy is to monitor the patient and evaluate whether there is any change over time of small PNs that initially do not cause any clinical symptoms.

If a PN is growing, surgery may be indicated, especially where the tumour is causing pain or deformity and/or intrudes on vital areas such as the trachea or bowel.[2] Of note though, by its very nature, PN is not a nodular tumour, and its web-like structure means that complete removal may not be easy or possible.[2,5] It is, therefore, necessary to consider that the surgical removal of a PN may result in related morbidity, bleeding, disfiguring, scarring, nerve damage, and/or loss of function, depending on PN size, location, and growth characteristics. Additionally, a recurrence of the tumour can occur.[5]

The decision to carry out surgery is usually made by an experienced MDT and may only occur after an investigation using ultrasound, MRI, and/or fluorodeoxyglucose-PET to ascertain the extent of both visible PNs and possible deeper, internal PNs, as well a potential evolution to a MPNST.[4,5] It is important, Azizi stressed, that the surgeon is highly skilled in PN removal, in general and specifically, for the location in the body where it arises. Such expertise may need to be sought outside of the centre where the patient is being treated, with discussions of complex cases even taking place at a national or international level when needed.

THE ROLE OF MITOGEN-ACTIVATED PROTEIN KINASE KINASE INHIBITORS IN THE TREATMENT OF PLEXIFORM NEUROFIBROMA

The *NF1* gene codes for neurofibromin, which interacts with the signal transduction protein rat sarcoma virus guanosine triphosphate (Ras-GTP), converting it to Ras-guanosine diphosphate. This results in decreased Ras-GTP mediated activation of the mitogen-activated protein kinase pathway, which is involved in the activation of a number of enzymes, including MEK. As this pathway ends in transcription factor activation, loss or disruption of the *NF1* gene (as seen in NF1), leads to increased mitogen-activated protein kinase pathway activation. As the pathway ends in transcription factor activation, this can lead to tumorigenesis. As Ras-GTP stays active with tumorigenesis, this pathway can be halted by targeting one of its components, which is where MEK inhibitors are useful.[6]

The MEK inhibitor selumetinib was recently approved in 11 countries, including the USA, European Union (EU) countries, and the UK, for the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged ≥3 years (≥2 years in the USA).[7] This followed Phase I[8] and II[9] open label trials (total N=74; aged 3–18 years) that reported tumour shrinkage and positive outcomes for symptoms, including pain intensity, interference with daily functioning, health-related quality of life, strength, and range of motion.[8,9]

The MEK inhibitor might come in as a game changer, explained Azizi, in situations where the PN is symptomatic and inoperable. This

occurs where surgery may imply a high potential for morbidity, such as nerve dysfunction and/or bleeding, or could only reduce, not completely remove, the tumour. Location is also a consideration as surgery is potentially a more valuable option for superficial tumours, and drug therapy might be more valuable for PNs that are deep-seated in the trunk, or in crucial positions such as the orbital region.[6]

Some adverse events (AE) have been reported with MEK inhibitors that patients and their parents or carers should be made aware of. In clinical trials, the most frequent AEs were: (acneiform) rash; nausea or vomiting; diarrhoea; asymptomatic increases in creatine phosphokinase levels; and paronychia.[8,9] In the selumetinib Phase II SPRINT trial, AEs led to a dose reduction in under a third of patients and treatment discontinuation in 10% (five patients) where AEs were considered possibly selumetinib-related.[9]

AEs tend to be most severe at the beginning of treatment, discussed Azizi. Accordingly, patients should be informed about potential side effects and their management, so they do not discontinue the drug inappropriately but only after medical consultation and decision. "On the other hand," Azizi explained, "we know that paronychia, for example, occurs later in the treatment. This can be annoying and might necessitate stopping the drug for a while until it heals, then you can restart."

"Almost all AEs are manageable," Azizi emphasised, "and the more experience you have with the treatment, the better it will be." Notably, specialists may be required to address and manage specific AEs caused by MEK inhibitors, such as a dermatologist for an eczematous rash in infants and acneiform rash in adolescents. These effects are common to the entire class of MEK inhibitors and, discussed Azizi, it is important to balance the risk–benefit ratio of drug treatment to the possible morbidity caused by surgery.

For those who are candidates for a MEK inhibitor, Azizi explained how he would use the medication for at least 2 years or longer, if tolerated and efficacious. This is partially because a response may only occur after a few months of treatment. For instance, in the Phase II SPRINT trial with selumetinib, the median time to response was 8 cycles (range: 4–20, each cycle lasting 28 days) and time to best response was 16 cycles (range: 4–36).[9] New data presented at the 2021 Children's Tumor Foundation (CTF) Congress, with up to 5 years use of selumetinib, is helping to further evaluate longer term efficacy, safety profile, and AE occurrence.[10-13]

THE FUTURE OF MITOGEN-ACTIVATED PROTEIN KINASE KINASE INHIBITORS

While surgery will remain the key treatment for PNs, the coming years, discussed Azizi, will answer a number of questions regarding the use of MEK inhibitors, and how these two approaches may be integrated to provide patients with the best possible treatment regimen for their disease. For instance, in PNs currently considered inoperable, a MEK inhibitor may be able to shrink them to a size where they can be surgically removed. Conversely, where a tumour is resectable, MEK inhibitors may stop them regrowing, suggesting that further research may be directed to explore use of these novel treatments in the neoadjuvant and adjuvant settings.

Among the questions that may be addressed by future research and real-world data collection, Azizi explained that it is of great interest to clarify when to stop treatment, since tumour regrowth has been observed in some patients when MEK inhibitor treatment was stopped.[9] As such, he discussed how it may be feasible for patients to have a trial period of stopping the MEK inhibitor and returning to a 'watch-and-wait' strategy, only restarting treatment if the tumour starts growing again.

More data will be available in the coming years as MEK inhibitor use becomes more common and the benefits and AE profile of long-term therapy will become clearer. At the moment, Azizi explained, possible late AEs of MEK inhibitors are not yet known (e.g., on development and fertility in 20 years' time). It will also be interesting to assess the potential positive or negative impact MEK inhibitor use will have on the rate of development of malignancies and other NF1 manifestations, such as cognition.

It is also necessary to evaluate alternative treatment schedules to better manage and prevent AEs and improve adherence, for instance, to a 5-days on, 2-days off regimen, with such studies ongoing. Finally, further

research is being directed toward the study of liquid formulations of MEK inhibitors, which may facilitate administration to younger patients, as well as those who have difficulty swallowing capsules due to cognitive problems. Research is also needed to assess the utility of MEK inhibitors in children <2 years since, Azizi highlighted, the youngest patients are usually the ones experiencing fast-growing PNs and potentially presenting with the highest need of a MEK inhibitor.

CONCLUSION

PNs occur in 30–50% of patients with NF1;[14] however, not all PNs need immediate treatment, and it is up to an experienced MDT to decide which approach should be used and when to start treatment. In complex cases, expertise should be sought on a national or international level.

Surgery is the current treatment of choice, if safely feasible, and the only option if malignisation to MPNST is suspected. This must be carried out by a surgeon with expertise in PN surgery, with specific consideration of the anatomical site. The recent market authorisation of a MEK inhibitor adds to the armoury against PNs as they can be used to treat inoperable, symptomatic patients. More data are being collected in both clinical practices and through clinical trials to better understand the safety and efficacy profile of the first approved MEK inhibitor, selumetinib, and of novel treatment options, combinations, and schedules to help support patients with NF1 who are developing PNs.

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