MEK INHIBITORS IN NF1

Children's Tumour Foundation
CONQUERING NF

The information provided below is a summary of the presentation given by Dr Geoff McCowage on 7 March 2020 at the NF Information Day in Sydney.

Dr Geoff McCowage is a senior paediatric oncologist at the Sydney Children's Hospital at Westmead and the CEO of Australasian Children's Cancer Trials.

He is the clinical lead for an Australian-based clinical trial co-funded by the Children's Tumour Foundation into the efficacy of MEK Inhibitors in treating NF-related tumours.

WHY ARE MEK INHIBITORS BEING TRIALLED?

This trial is intended to improve treatment options for people with NF1, specifically those with complex tumours like Plexiform Neurofibromas.

20-50% of children with NF1 will have a Plexiform Neurofibroma, although many will not require any treatment.

A small proportion of children may be offered treatment for pain or disfigurement, but up until recently, the only treatment available was surgery - which had limited success.

Between 10-15% of Plexiform Neurofibromas will develop into a Malignant Peripheral Nerve Sheath Tumours (MPNST), which do require treatment.

WHAT ARE MEK INHIBITOR DRUGS?

The two most common MEK Inhibitor drugs that have been used to treat NF1 patients are:

1. *Selumetinib*
2. *Trametinib*

Trametinib is TGA and PBS approved in Australia to treat melanoma, but there have been some encouraging results in treating plexiform neurofibromas and optic nerve gliomas in patients with NF1.

Overeseas trials have focussed on the use of Selumetinib to target plexiform neurofibromas. These have had some great success, with tumours responding positively to treatment – either reducing in size or remaining stable.

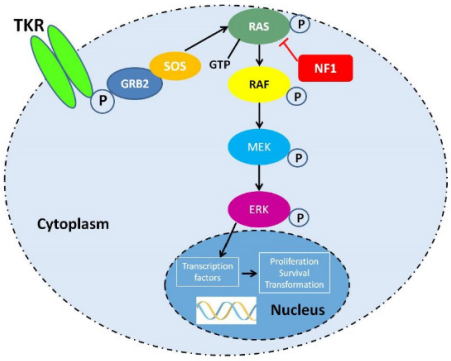
Treatments were given in monthly cycles with many patients showing the greatest improvement after 16-24 cycles. This indicates that the drug may require time to start working and there is a general caution about the cessation of treatment too early.

However, there was evidence that many patients who were experiencing pain, responded more quickly with pain levels reducing and in some cases disappearing

HOW DOES IT WORK & WHY?

Biochemical pathways are a chain of chemical reactions occurring within a cell. Some, like the pathway that NF1 sits in, are responsible for controlling cell growth. This is done by "regulation proteins".

The protein made by the NF1 gene works as an OFF switch for a pathway (RAS) which is responsible for sending messages from the outside surface of the cell to the central production hub (nucleus), a little like a courier delivering a package. When this protein is not functioning properly it sets off a chain reaction that causes cells to grow uncontrollably.



This diagram serves as a visual representation of how the biochemical pathway works.

When the RAS chemical gets stuck in the "ON" position, it means the brake that prevents cell multiplication (proliferation) from happening is not working, which then impacts each subsequent cell.

RAS ⟶ RAF ⟶ MEK ⟶ ERK causing cells to grow uncontrollably.

The current treatment drugs (Selumetinib and Trametinib) are aiming to interrupt this pathway of uncontrollable growth at the MEK level. Hence why they are called MEK Inhibitors.

In Australia, *Trametinib* will be trialled against 60 patients aged between 3 months and 25 years and at present, the trial is due to start enrolling in mid-late 2020.

WHAT ARE THE SIDE EFFECTS?

Generally, these drugs are better tolerated than "old fashioned" chemotherapy drugs because they do not require a central line for administration and as a result, the severity of side-effects is reduced.

- There is less likelihood of hair fallout, nausea or the need for platelet transfusions, but it is not without some side-effect.
- In adults with melanoma, they may experience heart or eye problems as a result of treatment, but in children the main side-effects seem to be skin-related. These include:
    - Acne
    - Rashes and paronychia (redness and soreness around fingers or toenails)
    - Folliculitis (infection of the hair follicle)

Treatment for skin complications include the use of antibiotics (including Doxycycline for acne), steroid creams or vinegar baths.

A positive side-effect amongst many children included improved muscle strength and range of motion after taking the MEK Inhibitors.

Many also experienced a reduction in their every day pain scores.

OTHER CONSIDERATIONS

Treatment Duration: It is likely that treatment will need to continue indefinitely. Some overseas studies have shown that ceasing the use of medication leads to a growth in tumour. That is why we are trialling this in Australia over a longer period of time.

Drug Availability: Trametinib is not readily available for patients and is an incredibly expensive treatment. Currently Novartis provide the drug to patients on compassionate grounds, but the goal of the trial is to prove it's effectiveness and ultimately advocate for it to be included in the PBS and therefore accessible to all.

Promising research out of the US shows that MEK Inhibitors could be beneficial for NF1 children with OPGs as well.

THE TINT MEK INHIBITOR CLINICAL TRIAL

Thanks to the support of Novartis (sponsoring the use of the drug for the duration of the trial), the Australian clinical trial will be testing the effectiveness of Trametinib on 60 Australian and New Zealand NF1 patients between the ages of 3 months and 25 years.

The trial will also test the hypothesis that the MEK Inhibitors help improve learning and social development outcomes for NF1 children and so another 120 children (of similar age to those on the drug) will also be invited to be part of the trial.

The trial will run for 5 years and will commence later in 2020. The trial is being co-funded by the Children's Tumour Foundation.

What will be assessed?

- Tumour size, pain and muscle responses
- Neurocognitive testing (learning and attention, which will be matched against an age-appropriate control group).

Recruitment for the trial:

- Opportunities to be part of the clinical trial will be a process coordinated by the participating hospitals. The five paediatric hospitals involved (RMCH, SCHW, QCH, and two other interstate hospitals yet to be confirmed) will invite patients to join the trial who qualify for the study.

- If you have an interest please let your specialist know and they will explain the criteria for selection.

- The CTF will have NO SAY in what patients will be enrolled. We are simply a co-funder and here to advocate to the government to make Trametinib accessible to all, should the 5 years trial prove that it is tolerable and provides benefit to NF1 Patients.

- The Children's Tumour Foundation will alert the NF Community when this information becomes available on our website, social media (follow us @ctfaustralia) and e-newsletter.

- To ensure you receive notifications of trial updates, please subscribe to our newsletter www.ctf.org.au

If you have any questions regarding this study and how you can get involved, our Support Team is available to help. You can reach them via phone on **(02) 9713 6111** or by email at **support@ctf.org.au**