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Cancer drugs could transform the lives of children with serious disfigurements

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Drugs normally used to treat cancer could reduce the disfigurements of thousands of children born with life-threatening blood vessel defects. The drugs are being trialed by researchers at Great Ormond Street Hospitalopens in new window (GOSH), based on the findings of MRC-funded geneticists.

The study, published in the Journal of Clinical Investigationopens in new window, involved testing the DNA of over 150 children with blood vessel defects including arteriovenous malformation (AVM).

In AVM, which affects hundreds of thousands of people across the globe, abnormalities in blood vessels lead to painful facial or other disfigurements, life-threatening bleeding and increased risk of complications like stroke. Until now, effective treatment options have been severely limited, with the only options being embolisation or surgery to try to stop growth, or reduce the swellings. However, these treatments often lead to the blood vessels growing back.

The scientists discovered that a proportion of patients had faults in the group of genes known to be involved in cancers but not previously known to be responsible for the correct formation of blood vessels in the womb.

Four genes were found to be faulty in different patients, but they were all on the so-called RAS/MAPK pathway which controls cell growth. This discovery enabled researchers to identify widely used cancer drugs

– MAPK pathway inhibitors, which are normally used to counteract faults in the RAS/MAPK genes in cancer cells – as a new potential treatment for AVM.

The scientists, at the MRC Institute of Genetics and Molecular Medicineopens in new window (IGMM) at the University of Edinburgh, modelled these mutations in zebrafish, as artery and vein development in these fish is regulated by similar mechanisms to those in humans. When tested in the lab on fish with abnormal blood vessels caused by these mutations, the drugs reduced the size of the blood vessel swellings and increased blood flow.

Dr. Elizabeth Pattonopens in new window, co-senior author of the study from the MRC IGMM, said: "The genes that cause this disease in humans can cause a similar disease in a small zebrafish, which gives us the opportunity to model the disease and test new treatment ideas in a basic research setting. What is exciting here is our testing in zebrafish found that a drug used to treat cancer could be repurposed to treat AVM. Because this drug is already in the clinical use, it means that it can more easily be used to treat conditions, such as AVM."

The drug will now be tested in an international clinical trial, planned to start next year.

Dr. Veronica Kinsler, co-senior author on the study who leads the clinical research at GOSH and the UCL Great Ormond Street Institute of Child Health, said: "This is a very exciting and potentially life-saving discovery. Understanding that these birthmarks are caused by faulty genes, and in particular that these can vary from patient to patient, is a huge leap forward in understanding the science behind AVM.

"The most exciting part is that there are already approved drugs available to use as part of clinical trials. We've seen some very encouraging results

in the lab and are hopeful that clinical trials in children will help those suffering with AVM."

Living with AVM

While formal clinical trials will be required before these drugs are routinely used in clinical care, the drugs have already been approved for other conditions and therefore can be considered on a compassionate basis in severe cases.

Nikki Lilly, was diagnosed with AVM when she was six years old, after being referred to Veronica Kinsler at GOSH. Since then, the 13-year-old has had more than 330 appointments and undergone dozens of procedures.

Nikki has high flow craniofacial AVM on the right-hand side of her face and, as part of Professor Kinsler's research, was found to have a fault in the RAS/MAPK genes. Based on the findings of the study, Nikki began taking medication. And in the six months since then, there has been no growth in her AVM. However, it is too early to say whether the treatment has been effective.

Nikki is an extraordinary girl, who has never been held back by her condition. A keen beauty and baking vlogger, she has nearly 300,000 subscribers on YouTube and is a reporter for children's channel CBBC. Her parents George and Tanya set up the Butterfly AVM Charity to support families affected by the condition. The charity has so far raised more than £250,000 and provided a grant to help fund this research.

Nikki said: "I was excited to take part in the study as I thought being able to take a drug to control or shrink my AVM would be a lot less painful than having regular operations.

"As I have only been on the drug for just over six months it's not enough time to really tell, but the first scans have been positive and show no further growth. I do feel very tired sometimes and I have a rash on my face and still get some nosebleeds, but none that have required transfusions."

More information: Lara Al-Olabi et al. Mosaic RAS/MAPK variants cause sporadic vascular malformations which respond to targeted therapy, *Journal of Clinical Investigation* (2018). DOI: 10.1172/JCI98589

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