MedicalXpress

In NIH trial, selumetinib shrinks tumors, provides clinical benefit for children with NF1

March 18 2020

Findings from a phase 2 clinical trial show that the drug selumetinib improves outcomes for children with the genetic disorder neurofibromatosis type 1 (NF1). In the trial, selumetinib shrank the inoperable tumors that develop with NF1 called plexiform neurofibromas, and children experienced reduced pain, improved function, and better overall quality of life after receiving the treatment.

The trial was led by intramural researchers in the Center for Cancer Research (CCR) at the National Cancer Institute (NCI), part of the National Institutes of Health. Results of the trial were published March 18, 2020, in the *New England Journal of Medicine*.

"Until now, no effective medical therapies have existed for children with NF1 and plexiform neurofibromas, and it's been a long journey to find a drug that can help them," said Brigitte Widemann, M.D., lead author of the study, and chief of CCR's Pediatric Oncology Branch, which developed and coordinated the trial. "While this is not yet a cure, this treatment is shrinking tumors and it's making children feel better and have a better quality of life."

The trial was sponsored by the NCI Cancer Therapy Evaluation Program (CTEP) and conducted by the NIH intramural program. Drugmaker AstraZeneca provided the study drug under a Cooperative Research and Development Agreement with NCI and supported correlated studies that

were part of the trial. The company worked closely with the researchers on the New Drug Application to gather the data that has been submitted by the company to the U.S. Food and Drug Administration (FDA). In addition, the Neurofibromatosis Therapeutic Acceleration Program (NTAP) provided funding to support patient enrollment at participating sites.

The trial enrolled 50 children ages 3 to 17 years with NF1-related plexiform neurofibromas in 2015 and 2016. The most common symptoms from the tumors were disfigurement, limitations on strength and range of motion, and pain. The children received selumetinib orally twice a day in 28-day cycles continuously, and assessments were performed at least every four cycles. The researchers used a novel approach to assess outcomes tailored to each patient's specific tumor-related symptoms, something no prior clinical trial directed at NF1 neurofibromas had done before.

As of March 2019, 35 children, or 70%, had a confirmed partial response (? 20% volumetric tumor shrinkage), and most of them maintained that response for more than a year. After a year on the treatment, children and parents reported lower levels of pain and clinically meaningful improvement in interference of pain in daily function, overall quality of life, strength, and range of motion.

"One of the most surprising findings of this trial was the impact the treatment had on pain," said Andrea M. Gross, M.D., of CCR, first author of the study. "It even helped patients who had been living with chronic, debilitating pain come off pain medications, which was not something we anticipated. So that was a really exciting finding."

Five children stopped receiving selumetinib because of side effects possibly related to the drug, and six children had disease progression. The most frequent side effects included nausea and vomiting, diarrhea,

and rashes.

The new study confirmed results of an earlier phase 1 trial that demonstrated for the first time that the drug could shrink large tumors. Dr. Widemann and her team have been studying selumetinib for NF1 since 2011. The drug works by blocking a protein called MEK that is part of the RAS signaling pathway, which is overly active in patients with NF1, leading to the growth of tumors. FDA granted orphan drug designation to selumetinib for the treatment of NF1 in 2018, and in 2019, the drug received FDA breakthrough therapy designation.

Plexiform neurofibromas have proven hard to treat. The tumors can grow quickly and become very large—up to 20% of a child's body weight. Surgery to remove the tumors is often not feasible because the tumors can be intertwined with healthy nerves and tissue. Tumors that have been partially removed by surgery also tend to grow back, especially in young children.

Dr. Widemann had been doing trials with different medications for NF1 since 2001 and was excited when she saw the first tumors shrink. She and her team are grateful to the many different groups and programs that have worked together to reach this point, including the NCI intramural and extramural programs, NTAP, and the Children's Tumor Foundation, all of which she said made this work possible. Most of all, however, the researchers want to thank the children and families who participated in the trial.

"There's a lot more to be done. Even though these children have tumor shrinkage, many still have disabling tumors," Dr. Widemann said. "But these findings are a big step forward and inspire us to work even harder towards additional progress in NF1 therapies."

The trial was conducted at the NIH Clinical Center in Bethesda,

Maryland, as well as three participating sites: Children's Hospital of Philadelphia, Cincinnati Children's Hospital Medical Center, and Children's National Hospital in Washington, D.C. Both the Children's Hospital of Philadelphia and Cincinnati Children's Hospital received additional funding for the trial from NTAP.

More information: *New England Journal of Medicine* (2020). DOI: 10.1056/NEJMoa1912735

Provided by National Cancer Institute