New cancer drug shows promise in pediatric patients with tumor-specific gene mutations

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A new cancer drug has proven safe and effective for pediatric patients with a rare tumor gene mutation, according to a study published today in *The Lancet*. The study tested the safety and dose of larotrectinib (LOXO-195) in pediatric patients with a mutation known as tropomyosin receptor kinases (TRK) that can occur in a variety of tumor types.

"This research highlights a paradigm shift in cancer care where we are identifying and treating tumors based on their genetic mutations, rather than just where they exist in the body, said Ramamoorthy Nagasubramanian, MD, an author of the study and division chief of pediatric hematology-oncology at Nemours Children's Hospital. "Additionally, this study represents a win for the field of pediatric research because the drug is being tested in children almost simultaneously with adults, when typically, pediatric research is years behind."

The multicenter, open-label, phase 1/2 study was conducted at eight sites in the U.S. and enrolled infants, children, and adolescents between the ages of 1 month and 21 years, with an average age of 4-5 years. The drug was administered orally among 24 patients with varying increasing dose concentrations adjusted for age and bodyweight. Of the patients enrolled, 17 had tumors with TRK fusions, while 7 of the patients did not have a documented TRK fusion.

Pediatric patients with TRK fusions had primary diagnoses of infantile fibrosarcoma, other soft tissue sarcoma, and papillary thyroid cancer.

Previously, the only treatments for many such patients has been chemotherapy, radiation, and, in some cases, surgery, all of which can have serious adverse effects.

The study found that LOXO-195 was well tolerated in patients and showed encouraging anti-tumor activity in all patients with TRK fusion-positive tumors. More than 90 percent of the patients with solid TRK fusion-positive tumors achieved "sustained tumor regressions." However, none of the patients with TRK fusion-negative cancers had an objective response. The recommended phase 2 dose was defined as 100mg/m2 for pediatric patients, regardless of age. The most common adverse events were mild elevations in liver enzyme concentrations, reduction in the number of mature blood cells, and vomiting.

With a median follow-up of eight months, all patients with TRK fusions, except for one, remainedon treatment or underwent potentially curative surgery.

"The TRK gene mutation can be common in pediatric cancers, especially those that are treatment resistant. When we saw this drug was showing promise of anti-tumor activity in adults with TRK fusion tumors, we were hopeful for a similar result for children. Both primary objectives of this study—safety and identifying dosing—were successfully met," said Nagasubramanian.

Clinical trials of LOXO-195 in adults, infants, children, and adolescents with acquired resistance to TRK inhibition are ongoing.

More information: Laetsch, T, et al. " Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study." *The Lancet* (2018): 29 March 2018. Web.

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