Tazemetostat shows early promise for children with certain relapsed or refractory solid tumors

October 30 2017

Children with relapsed or refractory malignant rhabdoid tumors, epithelioid sarcomas, or poorly differentiated chordomas with a particular genetic defect tolerated treatment with the investigational drug tazemetostat well and some had objective and durable responses, according to data from a phase I clinical trial presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Oct. 26-30.

"Malignant rhabdoid tumors and atypical teratoid rhabdoid tumors [ATRT; which occur in the brain] and other INI1-deficient tumors such as epithelioid sarcomas and poorly differentiated chordomas are extremely rare tumors in childhood," said Susan N. Chi, MD, director of the Pediatric Brain Tumor Clinical Trials Program and assistant professor in the Department of Pediatric Neuro-oncology at the Dana-Farber Cancer Institute and Boston Children's Hospital. "However, children with these tumors have a poor prognosis despite conventional treatment regimens and because of their rarity, there are no uniform treatment approaches."

INI-1 is a gene that is uniquely mutated in these types of tumors, Chi said. This mutation leads to deficiencies in DNA transcription and cell proliferation, so cancer cells use an alternate pathway to enable uncontrolled cell proliferation. The protein EZH2 is a component of this alternate pathway. Tazemetostat targets EZH2, thus inhibiting the

proliferative activity of cancer cells, she explained.

"This is the first ever clinical trial for children testing this class of drugs. The purpose of this study is to determine the highest dose tolerated, to characterize the side effects of this drug in children, and to assess the efficacy of this drug in select tumor types," Chi said.

Chi and colleagues enrolled patients from 6 months to 21 years old with INI-1 negative tumors in this multicenter phase I study. Patients received one of the seven dose levels of tazemetostat as an oral suspension twice daily. The investigators assessed objective responses every eight weeks.

Of the 46 patients treated so far, three—one with poorly differentiated chordoma, one with epithelioid sarcoma, and one with ATRT—had complete responses, and one patient with poorly differentiated chordoma had a partial response. The patient with the longest complete response remains in remission after more than a year on study, according to Chi.

"The children on this study experienced objective responses to this investigational drug that are durable at doses that appear to be well tolerated," noted Chi. "In fact, children have tolerated even higher doses than that in adults, thus demonstrating that children are not just "little adults" from the standpoint of drug dosing."

Adverse events were mostly mild to moderate and consistent with the safety profile observed in adults, Chi said. The study team also demonstrated that the same pharmacodynamic changes that were seen following drug treatment in laboratory models were seen in the blood of the patients.

The study has identified 1,200 mg/m2 tazemetostat given twice daily as the dose to go forward with the dose-expansion cohorts.

"We are encouraged by our findings that we may now have a novel agent that can be used to treat some of these very difficult-to-treat childhood cancers," Chi said. "For the rarest of tumors, especially in pediatrics, where specific and singular mutations may be the driving trigger, advances in the treatment of these tumors may offer insight to other more common tumor types potentially in children or adults or both," she added. The trial is currently in its dose-expansion phase.

A limitation is that this is a phase I study designed to evaluate safety and pharmacokinetics. "While we are encouraged to see clinical activity in children, we should remember that large phase II/III studies will provide more definitive assessments of clinical activity for investigational drugs," Chi noted.

Provided by American Association for Cancer Research