Medical Xpress

Targeted therapy shows effectiveness against a subtype of the brain tumor medulloblastoma

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Giles Robinson, M.D., is an assistant member of the St. Jude Department of Oncology. Credit: St. Jude Children's Research Hospital / Seth Dixon

A targeted therapy already used to treat advanced skin cancer is also effective against the most common subtype of the brain tumor medulloblastoma in adults and should be considered for treatment of newly diagnosed patients, according to research led by St. Jude Children's Research Hospital.

The drug, called vismodegib, is designed to block a key protein in the sonic hedgehog (SHH) signaling pathway. The pathway is normally active during fetal development and is inappropriately switched on in about 30 percent of medulloblastoma tumors, including about 60 percent of tumors in adults and 25 percent of tumors in children.

Medulloblastoma develops in the cerebellum at the base of the skull and involves four different subtypes, each with different genetic alterations. The tumor is diagnosed in as many as 400 children and adolescents annually in the U.S., making it the most common malignant pediatric brain tumor. Medulloblastoma is less common in adults, who account for about one-third of newly identified patients each year.

As expected, only patients with the SHH subtype responded to vismodegib; however, researchers also reported that the drug was not universally effective against all tumors in the subtype. The findings were published this month online ahead of print in the *Journal of Clinical Oncology*.

"While it was disappointing that not all medulloblastoma patients with the SHH subtype will benefit, for the right patients these results mark the beginning of a new era of targeted therapy for treatment of this tumor," said first and corresponding author Giles Robinson, M.D., an assistant member of the St. Jude Department of Oncology. "The findings also highlight the importance of ongoing research to identify the genetic alterations that define who the right patients are and help identify those most likely to benefit from this drug as well as those for whom different

therapy is needed."

Vismodegib received federal approval in 2012 for treatment of adults with advanced basal cell carcinoma. Preclinical research by St. Jude scientists helped to set the stage for trials of the drug in medulloblastoma patients. This Pediatric Brain Tumor Consortium study involved Phase II clinical trials that included 31 adults and 12 children with advanced medulloblastoma. Participants all had medulloblastoma that persisted or returned following standard treatment with surgery, radiation and combination chemotherapy.

Tumors shrank or disappeared completely for eight or more weeks in four study participants, including three adults, following vismodegib treatment. In 13 patients, or 41 percent of participants with SHH medulloblastoma, disease stabilized and tumors stopped growing for as long as 17 months during vismodegib therapy.

The findings led to the drug being included in the St. Jude clinical trial for newly diagnosed pediatric medulloblastoma patients aged 3 to 22 years old. Patients with SHH medulloblastoma receive vismodegib as maintenance therapy.

A detailed molecular analysis of patient tumors in this study confirmed scientific suggestions that the location of genetic alterations in the SHH pathway helped to predict vismodegib sensitivity, a proposition that had not been systematically evaluated until now. The drug is engineered to inhibit smoothened, which is a key protein in the SHH pathway. Vismodegib-sensitive tumors were characterized by alterations in genes like PTCH1, which precede the gene that encodes smoothened in the SHH pathway.

Researchers also identified other genetic alterations, particularly in the tumor suppressor gene p53, associated with limited effectiveness of the

drug against SHH medulloblastoma.

"This means complete genetic profiling of all sonic hedgehog medulloblastoma is needed to identify the patients who will benefit from vismodegib and those who are candidates for another therapy," Robinson said.

Such profiling will also help researchers develop combination therapies to overcome or avoid vismodegib resistance, he said.

"Tumor response to vismodegib in this study was transient, probably due to the development of drug resistance," Robinson said. "The finding that these tumors also contain other targetable mutations suggests several possible combination therapies that may increase sensitivity to vismodegib and combat drug resistance."

Overall survival for patients with SHH medulloblastoma is 70 percent, but the outlook is dismal for those with recurrent disease. In addition, current treatments often involve significant lifelong side effects that impact the ability of survivors to complete their education and live independently. "The great hope is that targeted therapies will help more patients survive with fewer long-term side effects," Robinson said.

More information: Vismodegib Exerts Targeted Efficacy Against Recurrent Sonic Hedgehog–Subgroup Medulloblastoma: Results From Phase II Pediatric Brain Tumor Consortium Studies PBTC-025B and PBTC-032, *J Clin Oncology* July 13, 2015. Epub ahead of print. DOI: 10.1200/JCO.2014.60.1591

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