Dabrafenib Promising in BRAF-Mutant Low-Grade Pediatric Glioma

Use of the targeted therapy dabrafenib resulted in a high overall response rate and was well tolerated in a small phase I/II study of pediatric BRAF V600-mutant low-grade glioma.

“The likelihood of curing a child with a low-grade glioma is very high,” said author Mark Kieran, MD, PhD, of the Dana-Farber Cancer Institute and Boston Children’s Hospital, in a press release. “In fact many children don’t suffer lifelong from the tumor but rather from the cognitive damage and secondary malignancies caused by radiation therapy.”

“The development of drugs that target the specific causative mutation of the tumor and avoid long-term toxicities may revolutionize the treatment of pediatric brain cancer,” Kieran said. According to the study, about 15% to 20% of patients with pediatric low-grade glioma have BRAF V600 mutations. These patients are known to have poorer survival and lower objective response rates. This was the first study to look at dabrafenib, an inhibitor of V600-mutant form of the BRAF kinase, in pediatric glioma.

The trial included 32 patients aged 2 to 17 with BRAF V600-mutant relapsed or refractory disease. Fifteen participants were in the phase I trial and 17 were in phase II. Four dose levels were tested in phase I up to and including the recommended phase II dose of 4.5 mg/kg/day in patients aged 12 or older, and 5.25 mg/kg/day in patients aged younger than 12, divided into two equal doses per day. The investigator confirmed overall response rate was 72%, with 1 patient achieving a complete response and 22 achieving a partial response. In 2 patients the tumor disappeared and in 11 patients the tumor shrunk by more than 50%. Eight patients remain on therapy. Additionally, 13 patients had stable disease lasting 6 months of longer; 11 of these patients remain on therapy.

Adverse events with dabrafenib were similar to those in adults, with frequent low-grade pyrexia, vomiting, fatigue, headache, and rash. The most frequent grade 3/4 adverse event was pneumonia. Studies in adults with BRAF V600E mutations have shown that combining a BRAF inhibitor with a MEK inhibitor reduces toxicity and produces more activity for a longer period of time.

“We want to make the response rate with dabrafenib even higher by combining it with a MEK inhibitor since that works in adults,” Kieran said. “Adding two drugs together normally produces twice as much toxicity. But much of the toxicity from the BRAF drug is inhibited by the MEK drug, so the combination is less toxic than either drug alone, which is unusual.”

Commenting on the findings, Michael Weller, MD, chairman of the department of neurology at the University Hospital Zurich in Switzerland, said: “The encouraging thing about this study is that this targeted treatment seems to work. At the moment in neuro-oncology we know almost everything about the molecular make-up of gliomas in adults and in children but we have not really been able to translate all this knowledge into an effective therapeutic agent.”

“These findings will have implications for clinical practice because many parents are willing to travel all around the world to get access to a promising treatment,” he continued. “We have almost no randomized data for brain tumors in children, at least for gliomas, because the tumors are too rare and the trials are difficult for ethical reasons.”
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